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Critical Issues in Critical Care

14

VLADIMIR KVETAN, MD, FCCM, AND
T. JAMES GALLAGHER, MD, FCCM, GUEST EDITORS

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To Cindy and Kristine

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Patients with cardiac and pulmonary insufficiency constitute a major percentage of admissions to the intensive care unit. In the last 25 years the technologic ability to administer nutritional therapy has grown enormously; in the same period, the realization that complex interrelationships exist between nutrition and metabolism in various disease states also has developed. This article discusses the metabolic support of patients with severe cardiac and pulmonary insufficiency. It also presents recent data suggesting that pharmacologic effects of nutrients have major implications for patients with severe cardiac and respiratory failure.

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Trauma anesthesia and critical care represent a continuum in the management of polytraumatized individuals. Initial airway management, resuscitation, and intraoperative care constitute only part of the professional role of the trauma anesthesia and critical care. Critical care transport and postoperative intensive care are of growing importance as initial patient survival improves. The organization of trauma care, role of the trauma anesthesiologist, and a journey through prehospital and intrahospital management are discussed.

Ethics in the Intensive Care Unit **423**
Christine L. Biedermann, A. Joseph Layon, and Robert D'Amico

This article describes four basic principles of medical ethics, the potential for conflicts among them, and the importance of moral reasoning. Using examples of ethical dilemmas that health care workers in the intensive care unit confront, a framework for approaching, understanding, and resolving these ethical conflicts is provided.

The Intelligent Anesthesiologist's Guide to the Language and Logic of Allocation **437**
Robert Baker, I. Alan Fein, and Martin A. Strosberg

As we approach the twenty-first century, the unconcern with resources seems increasingly to be associated with a semi-mythical past. Hospitals operate in the red, intensive care units are constantly full, and elective surgery is at risk for cancellation or rescheduling. With these concerns comes the need to master the language and logic of allocation, the language of bioethicists, economists, philosophers, and policy analysts. This article attempts to make the current language of allocation accessible to physicians and introduce them to some ideas and arguments in policy analysis circles.

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FOREWORD

Anesthesia and critical care have, by definition, always been closely related. Consequently, an anesthesiologist must know about and perform many of the same tasks in the operating room as the critical care specialist does in the intensive care unit. Accordingly, the American Board of Anesthesiology requires every diplomate candidate to have a significant amount of training and expertise in critical care.

This issue of *Anesthesiology Clinics of North America* on "Critical Issues in Critical Care" should be of intense interest to all anesthesiologists because it covers the complete breadth and depth of all important clinically relevant and new issues in critical care. Prior to deciding on their table of contents, the guest editors conducted a survey among residents, fellows, and critical care practitioners in a concentrated effort to find out what the intellectual and clinically practical needs were. The issue covers the care and support, in the most modern context possible, of every major organ and function.

Anesthesiology Clinics of North America is extremely fortunate to have Drs. Kvetan and Gallagher guest edit this issue. Both are and have been for many years directors of large, successful, and internationally recognized critical care programs. Both are very prominent members and have held high office in many of the important committees in the anesthesia and critical care communities. Both have authored many research and teaching publications and have lectured extensively in the area of critical care. Perhaps most illustrative of their present importance to the delivery and teaching of critical care, both are members and Dr. Kvetan chairs, the Task Force on Disasters of the Society of Critical Care Medicine; this Task Force was asked by the Office of the Army Surgeon General to recruit critical care teams to support Operation Desert Storm. Drs. Kvetan and Gallagher were able to put together 41 formal teams comprising 2000 anesthesiologists, surgeons, internists, and nurses from the best institutions in the United States. They were asked to do this enormous task, which created a new national resource for the United States and is relevant to any type of disaster, at the same time that they were putting this issue of *Anesthesiology Clinics of North America* together. It is truly remarkable that such a great quality issue on critical care was able to be published on time and is a great tribute to the talents of the guest editors. In summary, the expertise of the guest editors and the intrinsic importance of the subject matter at hand make "Critical Issues in Critical Care" a very compelling and important issue of *Anesthesiology Clinics of North America* for all anesthesiologists to read.

JONATHAN L. BENUMOF, MD
Consulting Editor

PREFACE

Anesthesiologists were always at the forefront of multidisciplinary critical care, and despite waning members in the terms of entry into this subspecialty in the 1980s, their continuous involvement in intensive care medicine is in the interest of patient care and quality training of residents and fellows. This issue of the Clinics touches on some topics of interest to anesthesia-based intensivists who are training and working in a multidisciplinary environment.

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Modern Concepts in Monitoring and Management of Respiratory Failure

Respiratory Mechanics

*N. Tony Eissa, MD,**
and Joseph Milic-Emili, CM, MD, FRSC†

During the last 20 years, there has been considerable interest in both invasive and noninvasive monitoring of cardiovascular function in critically ill patients, and many technological and conceptual advances have been made in this field. By contrast, respiratory monitoring has been essentially limited to measurements of blood gases and peak airway pressure. This is surprising considering the fact that ventilators equipped with built-in measuring devices and computers have been available for more than 15 years.[33] Despite the number of patients needing prolonged mechanical ventilation for varied clinical conditions, quantitative determination of respiratory mechanics is not routinely performed. The ability and use of such measurements would be expected to aid in clinical decision-making and the management of such critically ill patients. The quantitative changes in respiratory system mechanics that may occur in mechanically ventilated patients and the influence of this on the ability to discontinue ventilatory support or on ultimate patient outcome are largely unknown. Serial evaluation of respiratory system mechanics may aid in the investigation of these and other important clinical issues in the management of patients receiving mechanical ventilation. Our scanty knowledge of respiratory mechanics during mechanical ventilation probably reflects the preconception that measurements of respiratory mechanics in these patients are difficult to perform. In fact, in mechanically ventilated patients, a detailed analysis of respiratory mechanics can be performed readily with simple and commonly available equipment, namely, a pneumotachograph to measure flow, an integrator to obtain volume changes from the flow signal, and a pressure transducer to measure the pressure at the airway opening or, preferably, in the trachea some distance beyond the distal end of the endotracheal tube.[13] Several commercial ventilators permit direct measurements of these variables (e.g., Siemens 900C, Siemens-Elema AB, Solna, Sweden; and Puritan-Bennett 7200, Puritan-Bennett Corp., Kansas City, MD). With this equipment, it is possible to determine noninvasively the static and dynamic elastance of the respiratory system, the flow resistance of the

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respiratory system, airways, and thoracic tissues, and intrinsic positive end-expiratory pressure (PEEPi).[8, 19, 56, 61]

The respiratory system consists of two main parts: a gas exchanging organ, the lungs, and a pump that ventilates the lung. The pump consists of the chest wall, including the respiratory muscles, and the respiratory centers in the central nervous system that control the muscles used in moving the chest wall during breathing. Failure of any part of the system may lead to respiratory failure. Clearly, several mechanisms may account for respiratory failure in the same patient. Simplistically, however, it can be said that mechanical ventilation because of respiratory failure is required whenever the respiratory pump cannot cope with the mechanical loads that it has to overcome. Several recent reviews have studied the issue of respiratory monitoring in critically ill patients.[20, 39, 63, 74] Therefore, in this article we focus on some of the tests for assessing respiratory muscle function rather than attempting an exhaustive review, and discuss the various loads imposed on respiratory muscles (resistive, elastic, and intrinsic PEEP), together with other simple noninvasive measurements of ventilatory function. Results obtained with these tests in patients with chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) are outlined.

LUNG VOLUMES

Functional Residual Capacity

In mechanically ventilated patients, the functional residual capacity (FRC) can be measured by gas dilution techniques first adapted by Ramachandran and Fairly.[58] However, such measurements are technically difficult, and, hence, few measurements have been reported.[21, 34, 58, 73] Furthermore, these techniques do not measure the total thoracic gas volume but, rather, the gas contained in airspaces with open airways. Changes in total thoracic volume (including gases, liquids, and solids) can be estimated by noninvasive methods, such as radiography, CT, strain gauges, magnetometers, bellows pneumographs, and inductive plethysmographs. The last technique also permits partitioning of the respiratory movements into the motion of the rib cage and that of the abdomen-diaphragm.[63]

In normal subjects at rest, the end-expiratory lung volume (or FRC) corresponds to the relaxation volume (Vr) of the respiratory system, i.e., the lung volume at which the elastic recoil pressure of the respiratory system is zero.[1, 67] In critically ill patients, however, the FRC commonly exceeds Vr, a condition termed dynamic pulmonary hyperinflation.[27, 35]

Dynamic Hyperinflation

Dynamic hyperinflation exists whenever the duration of expiration is insufficient to permit the lung to deflate to Vr before the next inspiration.[27, 35] This tends to occur under conditions in which expiratory flow is impeded (e.g., increased airway resistance) or when the expiratory time is shortened (e.g., increased breathing frequency or inverse inspiratory/expiratory ratio ventilation). Expiratory flow also may be retarded by other mechanisms, such as contraction of the inspiratory muscles during expiration and expiratory narrowing of the glottic aperture.[67] At rest, under normal conditions, the end-expiratory elastic recoil pressure of the respiratory system (Pst,rs) is zero. When breathing takes place at lung volumes higher than Vr, the end-expiratory Pst,rs is positive. This pressure has been termed auto-PEEP[53] or intrinsic-PEEP (PEEPi).[61] In patients with severe airway obstruction, PEEPi is an important inspiratory load.

The presence of PEEPi implies that the end-expiratory lung volume during mechanical ventilation is greater than Vr, the difference between FRC and Vr being termed ΔFRC. During passive mechanical ventilation (e.g., controlled mechanical ventilation), ΔFRC (FRC − Vr) can be determined by inserting a prolonged expiratory time during a steady-state mechanical ventilation that permits the patient to exhale to Vr[59, 76] as shown in Figure 1. In patients with COPD or asthma with severe expiratory flow limitation, reaching Vr may require an expiratory time of as much as 40 seconds.[76] In patients receiving PEEP, the removal of PEEP during the prolonged expiration will permit measurement of the ΔFRC due to PEEP as well.[59]

Vital Capacity

Vital capacity is a simple test of thoracoabdominal mobility that is commonly measured in critically ill patients and is considered an important index for weaning.[64] In contrast, the inspiratory capacity is rarely studied in critically ill patients. This is surprising because breathing at rest usually involves only the inspiratory muscles, and, hence, inspiratory capacity should be a better index than vital capacity for predicting a patient's capacity to achieve an adequate tidal volume during spontaneous breathing.

FLOW-VOLUME LOOPS

Measurement of flow-volume loops during breathing at rest and with maximal efforts is an integral part of routine pulmonary function testing in stable patients

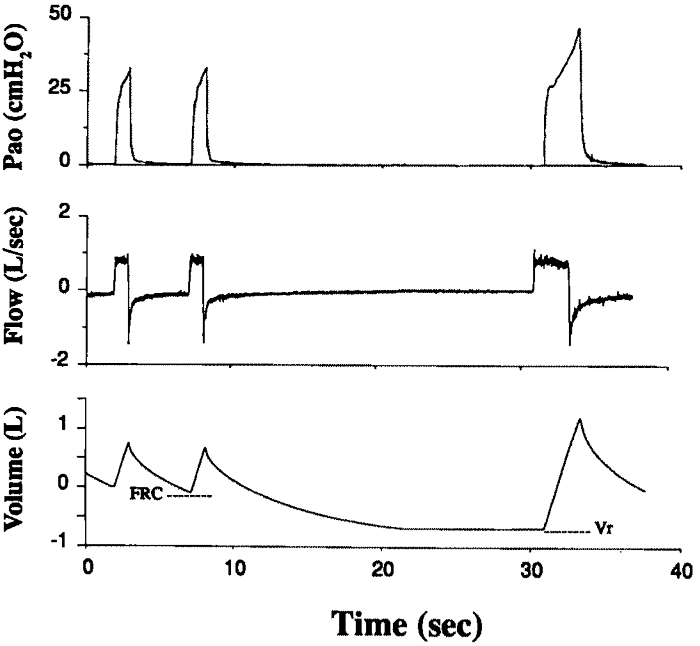

Figure 1. Records of pressure at the airway opening, flow, and changes in lung volume from a sedated-paralyzed COPD patient illustrating the measurement of change in FRC, which is the difference between end-expiratory lung volume (FRC) and relaxation volume of the respiratory system (Vr). A prolonged expiratory time was inserted during steady-state mechanical ventilation that allowed the patient to exhale to Vr. Change in FRC in this patient amounted to 0.673 L.

with respiratory disease. By comparing the flow-volume loops obtained during breathing at rest with those obtained during forced maximal inspiratory and expiratory efforts, the ventilatory reserve can be assessed. Such measurements are particularly useful in critically ill patients in whom the ventilatory reserve is often markedly reduced due to altered respiratory mechanics or abnormalities in respiratory muscle function or both.[35, 57] When possible, the respiratory status and evolution of these patients should be followed by studying their inspiratory and expiratory flow and volume reserve.

A useful way to detect dynamic hyperinflation and hence, PEEPi, is the analysis of the flow-volume relationship during a relaxed expiration.[26] When PEEPi is absent, the expiratory flow decreases smoothly to zero before the next mechanical inflation. By contrast, when PEEPi is present, there is flow throughout expiration, which is abruptly terminated by the next mechanical inflation such that the expiratory flow-time curve has a characteristic truncated appearance (Fig. 2).

MAXIMAL INSPIRATORY PRESSURE

Recently considerable progress has occurred in the assessment of diaphragmatic muscle function,[36] and several reviews are now available on this topic.[23, 28] However, assessment of diaphragmatic function is invasive because it involves measurement

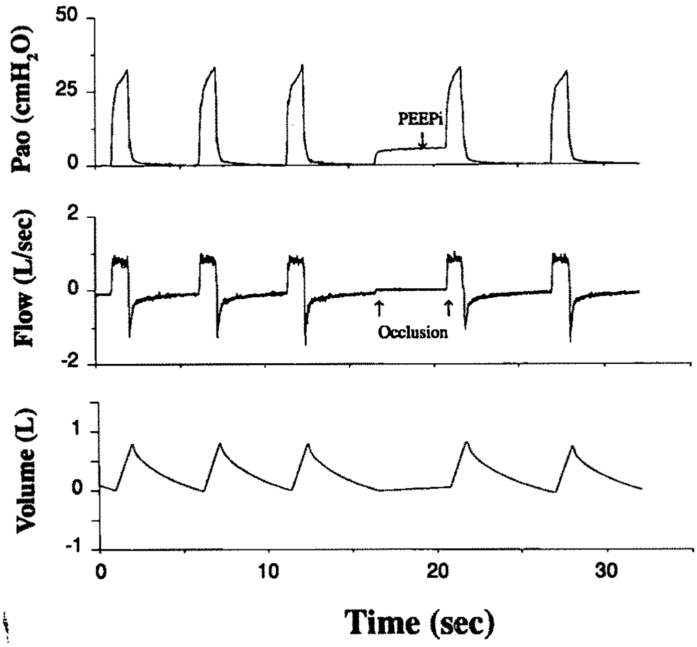

Figure 2. Records of pressure at the airway opening, flow, and changes in lung volume from the same COPD patient in Figure 1. Note that flow continues throughout expiration and is abruptly terminated by the onset of the next breath, indicating the presence of dynamic hyperinflation and intrinsic PEEP (PEEPi). PEEPi is measured by end-expiratory airway occlusion (*arrows*). Upon occlusion, the airway pressure rises and reaches a plateau that corresponds to the static end-expiratory elastic recoil pressure of the respiratory system (PEEPi). PEEPi in this patient amounted to 5.5 cm H_2O.

of esophageal and gastric pressures. By contrast, the inspiratory pressure developed at the mouth during a maximal inspiratory effort against an occluded airway (PI, max) is a simple noninvasive test of the contractility of the inspiratory muscles.[12] A decrease in PI, max may be due to hyperinflation, a change in thoracic configuration, neuromuscular disease, or fatigue.[12] Because PI, max represents the potential pressure that the inspiratory muscles can generate during spontaneous breathing, it has been considered a useful index to predict weaning outcome in mechanically ventilated patients.[5] However, the test has proved to be unreliable in that respect.[74] Furthermore, Multz et al[48] recently reported a poor reproducibility of the test in mechanically ventilated patients. This can be due to several factors. Although the test is simple, it requires good patient cooperation to obtain a true maximal effort. PI, max is conventionally measured with the patient making a maximal inspiratory effort at residual volume to maximize the mechanical advantage of the inspiratory muscles by increasing their operating length.[39] Because resting ventilation usually occurs well above residual volume, PI, max at FRC should be a better predictor of weaning outcome than PI, max at residual volume.

Breathing Pattern

Although monitoring of the heart rate and stroke volume in critically ill patients is done routinely, monitoring of their respiratory counterparts (breathing frequency and tidal volume) has been underused clinically. Most ventilators in current use permit direct measurement of spontaneous minute ventilation, frequency, and tidal volume (VT). The relationship between minute ventilation and arterial PCO_2 ($PaCO_2$) provides a good index of the ventilatory demands being placed on the respiratory system.[74] Because $PaCO_2$ is determined by the relationship between alveolar ventilation and CO_2 production ($\dot{V}CO_2$), a high minute ventilation in the presence of hypercapnia indicates the presence of dead space ventilation or increased CO_2 production or both. Maximum voluntary ventilation is the volume of air that can be inhaled and exhaled with maximum effort over 1 minute. The relationship between resting minute ventilation and maximum voluntary ventilation indicates the proportion of the patient's ventilatory capacity required to maintain a given $PaCO_2$ and also indicates the degree of reserve available for further respiratory demands. A resting minute ventilation of 10 L/min or less with the capability of doubling this value during a maximum voluntary ventilation maneuver is commonly considered to predict the success of weaning.[64] Low tidal volume (less than 300 mL) suggests that a weaning trial is likely to be unsuccessful.[74, 75] Such a low VT is often associated with tachypnea (i.e., rapid shallow breathing). Even in the absence of VT measurements, detecting a high respiratory rate (e.g., more than 22 breaths/min) is a sign of respiratory distress.[42] Although highly sensitive, tachypnea is a nonspecific sign, and further investigation is needed to determine the nature of the underlying disturbance.[42, 74, 75] In patients with severe airway obstruction, the fraction of inspiratory time (TI) relative to the total breathing cycle duration (TTOT) decreases.[4, 31] Because the inspiratory muscles are active mainly during inspiration, a decrease in TI/TTOT (also called respiratory duty cycle) decreases the burden on the inspiratory muscles and spares them from fatigue.[12, 23, 28]

MOUTH OCCLUSION PRESSURE

One of the major problems encountered in the study of the control of breathing has been to find a simple measure of the output of the respiratory center. Ventilation was originally used as a measure of this output, but it has the major disadvantage of being influenced by respiratory flow resistance, compliance, and PEEPi (if present), which may cause changes in ventilation that do not reflect variations in the respiratory center's activity. To avoid this problem, measurement of the rate of work (power) of the inspiratory muscles was proposed.[7] Measurements of oxygen cost of breathing and diaphragmatic electromyography have been used as well.[42] However, these measurements take time, are technically complex, and cause discomfort to the patient for they involve the use of esophageal electrodes, balloons, or both.

Measurements of the pressure generated by the inspiratory muscles at FRC against an occluded airway has been proposed as a useful alternative.[30, 42] Although measurement of maximal inspiratory pressures generated by patients against an occluded airway has long been used clinically to predict when a patient can be weaned from mechanical ventilation or extubation after anesthesia, systematic use of the mouth occlusion pressure as an index of the respiratory center's output was not made until 1973 by Grunstein et al.[30] It has since gained wide acceptance for clinical assessment of control of breathing because it is a simple noninvasive measure of neuromuscular inspiratory drive.[42] It consists of measurement of the pressure generated at the mouth in the first 0.1 second ($P_{0.1}$) of an inspiration made with the airway occluded at FRC.[42] $P_{0.1}$ reflects the inspiratory pressure potentially available for inspiration under the conditions of neurochemical stimulation of breathing prevailing during its measurement. The advantage of this method is that it is independent of lung mechanics.

The primary goal of mechanical ventilation is to reduce the increased inspiratory workload that precipitates or accompanies respiratory failure. However, it has been shown, that in patient-initiated mechanical ventilation, the mechanical work done by the patient frequently represents a high fraction of the total inspiratory work.[40, 71, 77] A close correlation was found by Marini et al[40] between $P_{0.1}$ and the patient's inspiratory work per liter of ventilation, and, hence, $P_{0.1}$ can be used as a simple noninvasive index to evaluate the inspiratory effort performed by the patient. During patient-initiated mechanical ventilation, $P_{0.1}$ can be measured readily by virtue of the fact that delay imposed by the demand valve systems of most ventilators provides an occlusion period long enough to permit measurement of $P_{0.1}$.[22, 40] The advantage of this approach is that every breath potentially provides an estimate of $P_{0.1}$.

In healthy subjects at rest, the values of $P_{0.1}$ are generally less than 2 cm H_2O.[70] In patients with respiratory disease, $P_{0.1}$ invariably increases,[42] particularly in patients with COPD who have acute respiratory failure.[2] In these patients, because of pulmonary hyperinflation, the inspiratory muscles operate at a mechanical disadvantage due to a decrease in their operating length.[66] Furthermore, because the diaphragm is flatter, a given tension (related to force) generates less pressure.[12] Accordingly, the high values of $P_{0.1}$ in these patients imply very high inspiratory muscle activity. Clearly, such high levels of inspiratory muscle activity cannot be sustained for a prolonged period without development of muscle fatigue.[23, 28] In fact, in patients with COPD who have acute respiratory failure, these high values of $P_{0.1}$ are associated with inspiratory muscle fatigue as assessed by diaphragmatic electromyography.[49]

The use of $P_{0.1}$ as a predictor of weaning outcome has been studied recently. Murciano et al[49] found that $P_{0.1}$ decreased from 7.4 ± 0.7 cm H_2O (mean ± SE) at the time of intubation to 3.9 ± 0.4 cm H_2O at the time of extubation in patients who were successfully weaned, whereas patients who failed a weaning trial showed no change in $P_{0.1}$ values, which at the time of intubation amounted to 6.6 ± 0.3 cm H_2O. Sasson et al[65] found that all patients who failed a weaning trial had $P_{0.1}$ values greater than 6 cm H_2O, whereas all patients who were successfully weaned had $P_{0.1}$ values less than 6 cm H_2O. In contrast, Montgomery et al[46] failed to find a significant difference in $P_{0.1}$ values between patients who were successfully weaned and those who failed a weaning trial. Clearly, further studies are required to evaluate the use of $P_{0.1}$ in mechanically ventilated patients.

Effective Inspiratory Impedance

It has been long been recognized that in the presence of mechanical limitations of breathing (e.g., increased elastance and flow resistance of the respiratory system), the ventilatory output reflects both how much the patient wants to breathe, an issue directly involving respiratory control, and how much his or her mechanical abnormality allows him or her to breathe, an issue that involves control of breathing only indirectly. To distinguish between the two mechanisms, measurements of the respiratory mechanical work rate have been used.[42] Indeed, an increased mechanical work rate to flow ratio, or increased mechanical work per liter of air ventilated, indicates the presence of mechanical abnormalities within the ventilatory pump. A simple noninvasive alternative is to measure the ratio of $P_{0.1}$ to minute ventilation or, more optimally, to VT/TI. The latter [$P_{0.1}$/(VT/TI)] has been termed the "effective inspiratory impedance."[42] Because this index is obtained by dividing the pressure generated during a fraction of an occluded breath by the mean inspiratory flow for an entire unoccluded inspiration, caution must be used in interpreting its significance. The effective inspiratory impedance has been found to be significantly lower in patients who are successfully weaned.[65]

RESPIRATORY LOADS

The breathing movements require work involving the following mechanisms: (1) elastic forces; (2) resistive forces resulting from flow of gas through the airways and viscoelastic forces attributable to stress adaptation units within the thoracic tissues (lung and chest wall)[8, 9, 18, 19]; and (3) in some patients, particularly those with airway obstruction, inspiratory work has to be exerted to overcome PEEPi.[31, 55] Because PEEPi imposes a threshold pressure that the inspiratory muscles must overcome before the onset of inspiratory flow, PEEPi can be regarded an inspiratory threshold load.[31, 55]

Intrinsic PEEP

Implications of PEEPi During Spontaneous Breathing. Figure 3 illustrates the increase in pressure required to overcome the elastic recoil of the respiratory system for the same tidal volume (20% of vital capacity) inhaled from Vr (34% of vital capacity) and from end-expiratory lung volume increase to 67% of vital capacity. As shown by the hatched areas, the elastic work increases approximately five-fold when the breath is inhaled from 67% of vital capacity (case B) relative to the breath

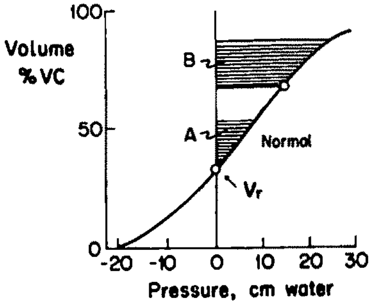

Figure 3. Volume-pressure diagram of the relaxed respiratory system showing the increase in elastic work caused by dynamic hyperinflation. VC = vital capacity, Vr = relaxation volume of the respiratory system. Hatched area A = elastic work for a breath that starts from Vr. Hatched area B = elastic work for a similar breath that starts from a volume 29% VC higher than Vr. In case B, the intrinsic PEEP is 15 cm H_2O, as indicated by the upper circle.

taken from Vr (case A). Clearly, dynamic hyperinflation implies an increase of both elastic work and inspiratory muscle effort. Furthermore, as lung volume increases, there is a decreased effectiveness of the inspiratory muscles as pressure generators, because the inspiratory muscle fibers become shorter (force-length relationship) and their geometric arrangement changes.[66]

Under normal conditions (case A in Fig. 3), the end-expiratory elastic recoil pressure of the respiratory system is zero. In this instance, as soon as the inspiratory muscles contract, the alveolar pressure becomes subatmospheric and gas flows into the lungs. When breathing takes place at lung volumes higher than Vr, the end-expiratory elastic recoil pressure (PEEPi) is positive (15 cmH_2O in case B of Fig. 3). When PEEPi is present, onset of inspiratory muscle activity and onset of inspiratory flow are not synchronous; inspiratory flow starts only when the pressure developed by the inspiratory muscles exceeds PEEPi because alveolar pressure only then becomes subatmospheric. In this respect, PEEPi acts as an inspiratory threshold load on the inspiratory muscles,[31, 35, 55] which are already operating under mechanical disadvantage.

Implications of PEEPi During Mechanical Ventilation. As mentioned previously, the putative role of mechanical ventilation is to reduce the activity of the inspiratory muscles to tolerable levels during patient-triggered mechanical ventilation (e.g., assisted mechanical ventilation, pressure support). This end is not achieved in patients who exhibit high PEEPi because the inspiratory effort required from the patient to trigger the ventilator may be excessive.[55, 69] In contrast, during controlled mechanical ventilation, all of the work of breathing is done by the ventilator. Nevertheless, PEEPi must be taken into account for correct measurement of respiratory compliance[61] and more importantly in terms of adverse effects on venous return and cardiac output.[53] Furthermore, patients with high PEEPi are implicitly difficult to wean from mechanical ventilation and become ventilator-dependent.[35]

Methods to Measure PEEPi. In mechanically ventilated patients, however, the increase in end-expiratory airway pressure will not normally register on the ventilator manometer.[53] During exhalation, the ventilator manometer is exposed to ambient pressure because the exhalation valve is open. Only resistance from the valve or applied PEEP will register on the ventilator manometer. Despite the fact that distal airway pressure may be positive throughout exhalation, the manometer will not reflect the increased pressure unless the expiratory port is occluded. If the expiratory port is occluded at end-expiration, distal airway pressure and circuit pressure equilibrate, and PEEPi will be reflected on the ventilator manometer. Figure 2 illustrates this method in a patient with COPD. Occlusion was done at end-expiration using the end-expiratory hold button on the servo 900C ventilator. The airway pressure rises and reaches a plateau that corresponds to PEEPi. An external valve is needed to perform occlusion in patients with ventilators that are not equipped with end-expiratory hold buttons.

In spontaneously breathing patients, PEEPi can be determined as the negative deflection in esophageal pressure from the start of inspiratory effort to the onset of inspiratory flow.[31, 55] This pressure has been termed dynamic PEEPi.[31, 55] Values of dynamic PEEPi are usually lower than those obtained by the end-expiratory occlusion technique described previously (static PEEPi). Static measurement of PEEPi necessarily reflects alveolar pressure after readjustment of dynamic regional volume and pressure differences due to time-constant inequalities within the lung (pendelluft). In other words, in this situation, PEEPi reflects the equilibrium or static increase in end-expiratory Pst,rs caused by dynamic hyperinflation. In the presence of pendelluft (and, hence, regional difference in PEEPi), it is axiomatic that static PEEPi should exceed the lowest regional alveolar pressure present at the end of an unoccluded expiration. By contrast, the dynamic PEEPi should reflect the lowest regional end-expiratory alveolar pressure (or regional PEEPi) within the lung. Indeed, as soon as esophageal pressure during inspiration balances the lowest regional PEEPi, air begins to flow into the lung. In the instance of a mechanically uniform lung, static and dynamic PEEPi should be identical, but in the presence of time-constant inhomogeneities within the lung, static and dynamic PEEPi differ, the latter reflecting the lowest regional PEEPi. In a recent study of patients with severe COPD, Petrof et al[55] found that dynamic PEEPi represented, on average, 57% of static PEEPi.

Another approach for measuring PEEPi in spontaneously breathing patients is by monitoring changes in thoracic volume using respiratory inductive plethmography while adding continuous positive airway pressure.[32, 55] The level of continuous positive airway pressure at which thoracic volume starts to increase should correspond to PEEPi.[32]

Compliance

Static Compliance of the Respiratory System. Reduced static compliance of the respiratory system (Cst,rs) implies an increase in the elastic load on the respiratory muscles. Cst,rs in mechanically ventilated patients is conventionally measured by dividing VT by end-inspiratory Pst,rs obtained by end-inspiratory airway occlusion until a plateau is reached (usually after several seconds). In this situation, the adequacy of respiratory muscle relaxation is indirectly assessed by the presence of a plateau in airway pressure during the occlusion. This approach assumes that the end-expiratory lung volume during mechanical ventilation corresponds to the relaxation volume of the respiratory system. However, this assumption is often not valid. This problem can be easily overcome by performing airway occlusion at end-expiration (see Fig. 1) in addition to end-inspiration (Fig. 4). Cst,rs is then computed as VT divided by the difference in airway pressure between end-inspiratory and end-expiratory occlusions.[61] Failure to recognize and measure PEEPi leads to underestimation of Cst,rs measurements.

The previously described measurements require patients to be relaxed, otherwise the use of an esophageal balloon to measure pleural pressure is needed. The esophageal balloon technique has been validated in critically ill patients.[24, 49] Cst,rs varies considerably with changes in tidal volume.[8, 17, 19] Therefore, its measurement becomes useful mainly to follow the progress of a given patient at a given ventilation setting. An increase in Cst,rs in this situation can be taken as a sign of improvement and vice versa.

Static Volume-Pressure Relationship of the Respiratory System. The elastic properties of the respiratory system may be best assessed by constructing the static volume-pressure relationship of the respiratory system obtained under conditions in which airflow is absent and respiratory muscle relaxation is complete. This measurement can be performed readily in relaxed mechanically ventilated patients using the rapid airway occlusion technique.[8, 37, 59] In this procedure, VT is changed for one breath (test breath), and end-inspiratory airway occlusion for 2 to 5 seconds will give rise to a plateau pressure that corresponds to the end-inspiratory Pst,rs (Fig. 4). If a series of end-inspiratory airway occlusions is performed at different VTs, the static volume-pressure relationship can be constructed by plotting Pst,rs against the corresponding inflation volume. Relaxation of the respiratory muscles can be achieved by administration of muscle relaxants or sedatives or both. The use of mechanical hyperventilation to relax patients by reducing their $PaCO_2$ and, hence, their respiratory drive is problematic because hypocapnia will lead to increased airway resistance.[13] In newborns, the persistence of the Breuer-Hering inflation reflex entails complete respiratory muscle relaxation during the procedure.[47]

The airway occlusion technique mentioned previously is an appealing approach in comparison with the earlier method (super-syringe technique) used to construct

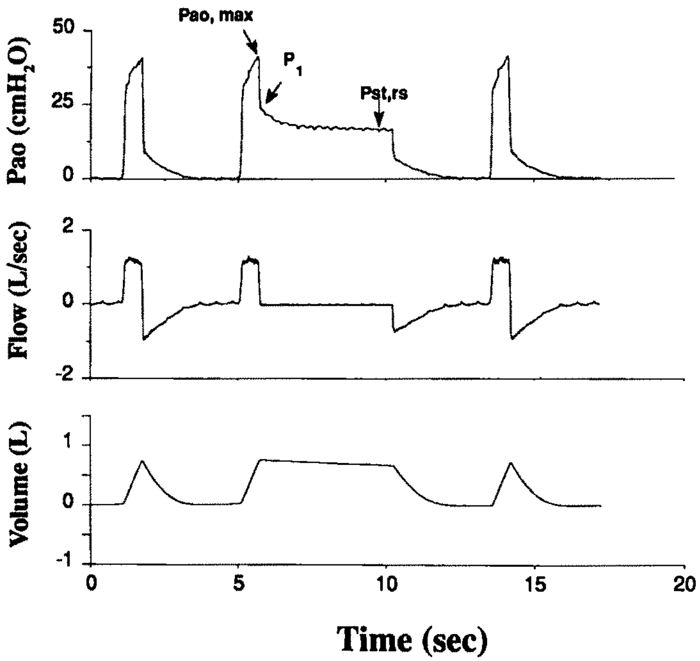

Figure 4. Records of pressure at the airway opening, flow, and changes in lung volume from a sedated-paralyzed ARDS patient, which illustrate the technique of rapid airway occlusion. After end-inspiratory airway occlusion there is an immediate drop in pressure from Pao, max to P_1, followed by a slow decay to a plateau value that represents static elastic recoil pressure of the respiratory system (Pst,rs). The decrease in pressure from Pao,max to P_1 includes resistive pressure attributable to the endotracheal tube.

static volume-pressure curves in mechanically ventilated patients,[25, 41] because it is simple, does not require disconnecting the patient from the ventilator, and minimizes the artifact due to continued gas exchange during the procedure.[37, 59]

Dynamic Compliance of the Respiratory System. Effective dynamic compliance of the respiratory system (Cdyn,rs) is commonly determined by dividing VT by the difference between peak airway pressure (Pao,max) and end-expiratory airway pressure.[20] This variable clearly does not represent the true Cdyn,rs because Pao,max includes a resistive pressure component.[8, 19, 20] Furthermore, this measurement does not take into account PEEPi. However, it is a useful index of the effective inspiratory *impedance* of the respiratory system.[43] The true Cdyn,rs is obtained by dividing VT by the difference in pressure between the end-inspiratory and end-expiratory points of zero flow. The end-inspiratory point of zero flow corresponds to the airway pressure immediately following end-inspiratory occlusion (P_1) (Fig. 4),[8, 19] whereas the end-expiratory point of zero flow corresponds to dynamic PEEPi.[31, 55] P_1 can be measured readily breath-by-breath by applying a brief end-inspiratory pause (e.g., 0.1 sec), available on most ventilators. In both normal subjects[8] and critically ill patients,[19] Cdyn,rs is markedly flow, volume, and TI dependent. Compliance is simply the reciprocal of elastance.

Flow Resistance

Currently, there are four approaches for measuring flow resistance: (1) the elastic subtraction method,[51] (2) the interrupter method,[51] (3) the forced oscillation method,[16] and (4) the plethysmographic method.[15] For obvious reasons, the last approach cannot be applied in mechanically ventilated patients. In the past, the forced oscillation technique could not be applied in these patients because of technical problems caused by the tracheal tube; however, a possible solution has been proposed recently.[50] The technique of rapid airway occlusion during constant flow inflation, previously described in detail,[8, 19] is essentially a combination of two of the basic approaches for measuring flow resistance described in 1927 by von Neergaard and Wirz: the interrupter and the elastic subtraction methods.[51] This technique was originally proposed by Rattenborg in 1956.[60] A virtue of the technique is that flow resistance can be measured at a fixed inspiratory flow but different tidal volumes, or at fixed tidal volumes but different inflation flows. Furthermore, with this approach, the measurements can be carried out with any preselected previous lung-volume history. This technique is appealing both for its simplicity and because it provides a comprehensive on-line assessment of respiratory mechanics. It cannot only be applied in patients with relaxed respiratory muscles but also in patients who trigger the ventilator, provided that most of the inspiration is passive (relaxed). Furthermore, if pleural pressure is measured by the use of an esophageal balloon, measurements could be partitioned into lung component and chest wall component.

This technique permits measurements of the interrupter resistance, which, in humans, is thought to reflect airway resistance,[9, 18] and the effective additional resistance due to viscoelastic properties of the respiratory system and time-constant inequalities. The latter is also called tissue resistance[44] and is flow, volume, and TI dependent.[8, 19]

Endotracheal Tube Resistance. It should be stressed that in mechanically ventilated patients, the endotracheal tube contributes markedly to total flow resistance.[3, 26] The flow resistance offered by the endotracheal tubes increases markedly with increasing flow and varies with the size of the tube.[26]

CLINICAL IMPLICATIONS

Monitoring and management of critically ill patients should be tailored to the individual patient. Therefore, we discuss separately two common disorders, namely, COPD and ARDS.

Chronic Obstructive Pulmonary Disease

PEEPi and dynamic hyperinflation are almost invariably present in patients with severe COPD and appears to have a paramount role in causing hypercapnic respiratory failure. In patients with COPD, a vicious circle exists: the inspiratory flow resistive work is invariably increased due to airway obstruction, which in turn promotes dynamic hyperinflation with a concomitant increase in elastic work and impaired mechanical performance of the inspiratory muscles.[66] With increased severity of COPD, a critical point is eventually reached at which the inspiratory muscles become fatigued.[4]

PEEPi in Stable Patients with COPD. Haluszka et al[31] have recently studied the prevalence and magnitude of PEEPi, and its correlation to pulmonary mechanics and $PaCO_2$ in 96 patients with COPD with varying degrees of airway obstruction. PEEPi was determined as the negative deflection in esophageal pressure from the start of inspiratory effort to the onset of inspiratory flow. A significant correlation was found between PEEPi and forced expired volume in 1 second and between PEEPi and pulmonary flow resistance. These results confirm that increased pulmonary flow resistance promotes the development of dynamic hyperinflation. Although pulmonary flow resistance is paramount in determining dynamic hyperinflation, other factors, such as respiratory frequency, VT, and the braking action of the glottis and of the inspiratory muscles during expiration should also have a role.[31] In the presence of a high pulmonary flow resistance, an increase in respiratory frequency and VT makes patients with COPD especially prone to the development of dynamic hyperinflation with a concomitant increase in work of breathing. When the magnitude of the inspiratory efforts approaches the critical level causing fatigue,[4] the patients reduce their VT and, hence, hypoventilate. This results in chronic hypercapnia.[70] If such patients are asked to restore VT to normal values voluntarily, they invariably experience diaphragmatic fatigue,[4] indicating that the shallow breathing pattern is an adaptive strategy that is used to avoid inspiratory muscle fatigue.

PEEPi in Patients with COPD Acute Respiratory Failure. The highest values of PEEPi observed in stable patients with COPD range between 7 and 9 cm H_2O.[31] In patients with COPD with acute respiratory failure, higher values have been reported: as much as 13 cm H_2O during spontaneous breathing[55] and 22 cm H_2O during mechanical ventilation.[6] Such high values of PEEPi have profound consequences on the energetics of breathing as shown schematically in Figure 5. Acute ventilatory failure in patients with COPD is usually triggered by a predisposing event (e.g., airway infection). As a result, there is an acute increase in airway resistance, and expiratory flow limitation becomes more severe. The increased resistance causes increased work of breathing and promotes dynamic hyperinflation. The latter is further exacerbated by the tachypnea that is invariably present in acutely ill patients with COPD. Dynamic hyperinflation promotes an increase of elastic work of breathing, which is due to PEEPi and decreased lung compliance. The latter is reduced because at high lung volume, the slope of the static volume-pressure curve of the lungs decreases (Fig. 3).[57] The increased resistive and elastic

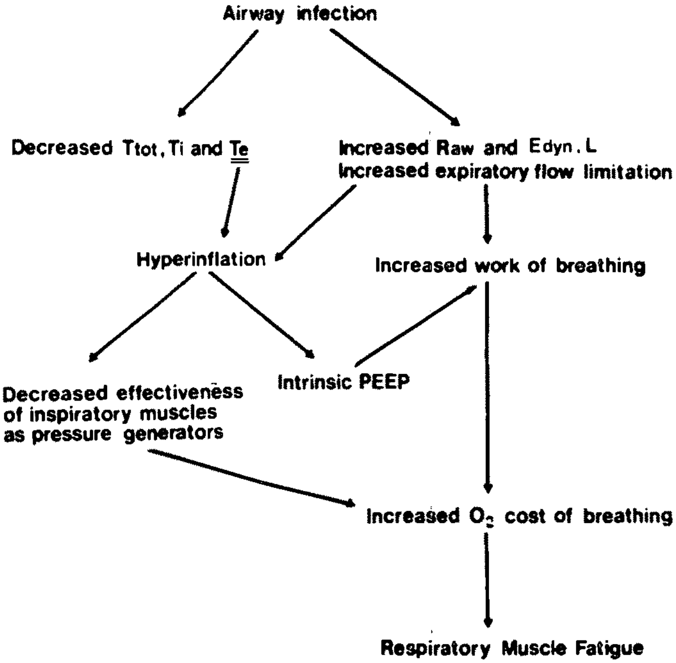
Airway infection
Decreased Ttot, Ti and Te
Increased Raw and Edyn.L
Increased expiratory flow limitation
Hyperinflation
Increased work of breathing
Decreased effectiveness of inspiratory muscles as pressure generators
Intrinsic PEEP
Increased O2 cost of breathing
Respiratory Muscle Fatigue

Figure 5. Scheme of the pathophysiology causing acute ventilatory failure in COPD patients. Edyn = L lung elastance (reciprocal of lung compliance), Raw = airway resistance, Te = expiratory time, Ti = inspiratory time, Ttot = total breathing cycle duration.

work of breathing, increased work due to PEEPi in association with the impaired inspiratory muscle performance, leads eventually to inspiratory muscle fatigue. As a result, the patient needs to be ventilated mechanically.

Strategies to Reduce the Inspiratory Load Caused by PEEPi. As implied in Figure 5, treatment of patients with COPD with respiratory failure should be directed to reduce the respiratory frequency (and, hence, increase expiratory time) and to decrease the flow resistance. To the extent that tachypnea is due to fever or airway infection or both, resolution of these conditions by conventional treatment should be beneficial. Similarly, administration of bronchodilator drugs may be useful in reducing both flow resistance and PEEPi. A less conventional but promising approach to manage PEEPi is the external application of positive pressure. Indeed, continuous positive airway pressure has been found to reduce the magnitude of the inspiratory muscle efforts and the work of breathing in stable patients with severe COPD.[55] In addition, continuous positive airway pressure administered through a face or nasal mask[54] also may be of therapeutic benefit during an acute exacerbation of COPD in nonintubated patients. Conceivably, the early use of continuous positive airway pressure in this setting could preclude the need for intubation and mechanical ventilation in some patients with COPD. It should also be noted that application of external PEEP during patient-initiated mechanical ventilation can counterbalance and reduce the inspiratory load imposed by PEEPi.[55, 69] To avoid pulmonary hyperinflation with increasing PEEP, lung volume can be monitored using a magnetometer or respiratory inductance plethysmography.[55, 69]

Adult Respiratory Distress Syndrome

Reduced Cst,rs (increased stiffness) is generally considered a hallmark of ARDS.[8, 21, 34, 41] Reduced lung compliance in ARDS has been attributed to pulmonary edema,[38] loss of ventilated lung units,[68] and increased lung surface tension.[56] Katz et al[34] reported reduced compliance of the chest wall in patients with acute respiratory failure of different etiologies, including ARDS. This was attributed to the presence of abdominal distension, chest wall edema, pleural effusion, and restrictive bandages.

Slutsky et al[68] noted that after inducing pulmonary edema with oleic acid in dogs, the volume-pressures curves of the lungs were shifted downward and to the right (i.e., reduced compliance). However, when volume was determined in terms of rib cage expansion (anteroposterior diameter) using a magnetometer, the curves obtained before and after administration of oleic acid were virtually superimposed. Because the changes in rib cage magnetometer signal reflect the changes in total volume of the thorax (gas, liquid, and solid), these findings are consistent with the concept that the presence of pulmonary edema does not alter the intrinsic compliance of the lung tissue, but rather that the excess edematous fluid simply competes with gas for space. In fact, recent research by Gattinoni et al[25] in which CT was used has demonstrated that the lungs in patients with ARDS are not homogeneously affected, and that volume-pressure curves performed on these patients investigate only healthy or recruitable zones that have essentially normal intrinsic properties. Thus, in ARDS, the clinician might be effectively managing a functionally small lung ("baby lung") rather than a stiff lung of normal dimensions.

These findings have important clinical implications. Large tidal volumes (10–15 mL/kg) and high levels of PEEP (10–15 cm H_2O) are often used in the management of ARDS to improve arterial oxygenation.[21, 34, 72] Several mechanisms have been postulated to account for this effect: recruitment of previously collapsed alveolar units,[38] reduction of cardiac output,[11] improvement in ventilation-perfusion mismatch,[10] and redistribution of lung water.[52] In the absence of significant alveolar recruitment, application of PEEP results in hyperinflation of the functional lung units and increased risk of pulmonary barotrauma.[17, 21, 70] Application of high levels of PEEP or large tidal volumes in patients whose lungs are severely affected (i.e., with "baby lungs") can be expected to result in dangerous alveolar overdistension.[17, 70] Of eight patients with ARDS studied on zero end-expiratory airway pressure (ZEEP) and with variable VTs, six patients showed evidence of alveolar overdistension (i.e., reduced compliance) when they were ventilated with VTs within the conventionally recommended range (10–15 mL/kg). The stiffer the patient's respiratory system, the less VT needed to reach alveolar overdistension.[17]

Figure 6 illustrates the static volume-pressure curves in two patients with ARDS obtained both on ZEEP and on PEEP of 10 cm H_2O. Lung volume is expressed relative to the FRC on ZEEP. Changes in FRC due to PEEP were determined using the procedure shown in Figure 1. In the patient of panel A, the static volume-pressure curve on ZEEP exhibited a convexity toward the x-axis, indicating progressive alveolar recruitment with increasing inflation pressure. Application of 10 cm H_2O of PEEP in this patient resulted in an upward shift of the static volume-pressure curve, which reflects for the most part recruitment of new lung units.[20, 34, 70] By contrast, in the patient of panel B, the static volume-pressure curve on ZEEP reflected a curvilinear relationship with concavity toward the x-axis, indicating that this patient was already operating on the flat portion of the volume-pressure curve. With application of PEEP, the data points moved along a fixed volume-pressure relationship, indicating no alveolar recruitment but, rather, overdistention of lung units with increased risk of pulmonary barotrauma. These results imply that measurement of the static volume-pressure curve can provide useful information about the potential response to added PEEP in terms of alveolar recruitment and risk of pulmonary barotrauma.[70]

Apart from pulmonary barotrauma, severe alveolar overdistension has been shown to cause acute lung injury characterized by pulmonary edema through epithelial and endothelial damage.[14] Surfactant deficiency was also produced in the lungs of dogs by ventilation with large VTs.[29] Because the same end-inspiratory lung volume can be reached by various combinations of PEEP and VT, further studies are needed to elucidate the optimal combination of PEEP and VT.

PEEPi in Patients with ARDS. Moderate values of PEEPi (up to 6.5 cm H_2O) also have been reported in patients with no history of chronic airway obstruction during mechanical ventilation, including patients with ARDS.[6, 70] Although in patients with COPD, PEEPi is caused primarily by expiratory flow limitations,[31, 55] the nature of PEEPi in patients with ARDS is not clearly understood. In the absence of respiratory muscle activity, the rate of lung deflation is determined by the elastic recoil pressure stored during the preceding lung inflation and the opposing total flow resistance offered by the respiratory system (including endotracheal tube, ventilator tubing, and additional equipment, if any).[3, 45] Accordingly, the stiffer the respiratory system (i.e., decreased compliance), the faster the rate of lung emptying. Conversely, increased flow resistance will impede the rate of lung deflation. Thus, it seems likely that PEEPi in ARDS is due to increased expiratory flow resistance.

Flow Resistance in Patients with ARDS. Adult respiratory distress syndrome is not only a disease characterized by reduced compliance but also entails increased flow resistance. Indeed, recent research has shown that patients with ARDS have an increase of both airway and tissue flow resistance.[6, 18, 19, 78] Factors leading to increased airway resistance in ARDS include airway flooding, reduced lung volume, vagal reflexes, and bronchial hyperreactivity.[18, 78] Tissue resistance is markedly flow, volume, and TI dependent.[8, 19] It is particularly prominent at low respiratory frequencies (< 15 breaths/min), at which it accounts for most of the total resistance of the respiratory system.[19] At high frequencies (> 30 breaths/min), it becomes negligible.[19]

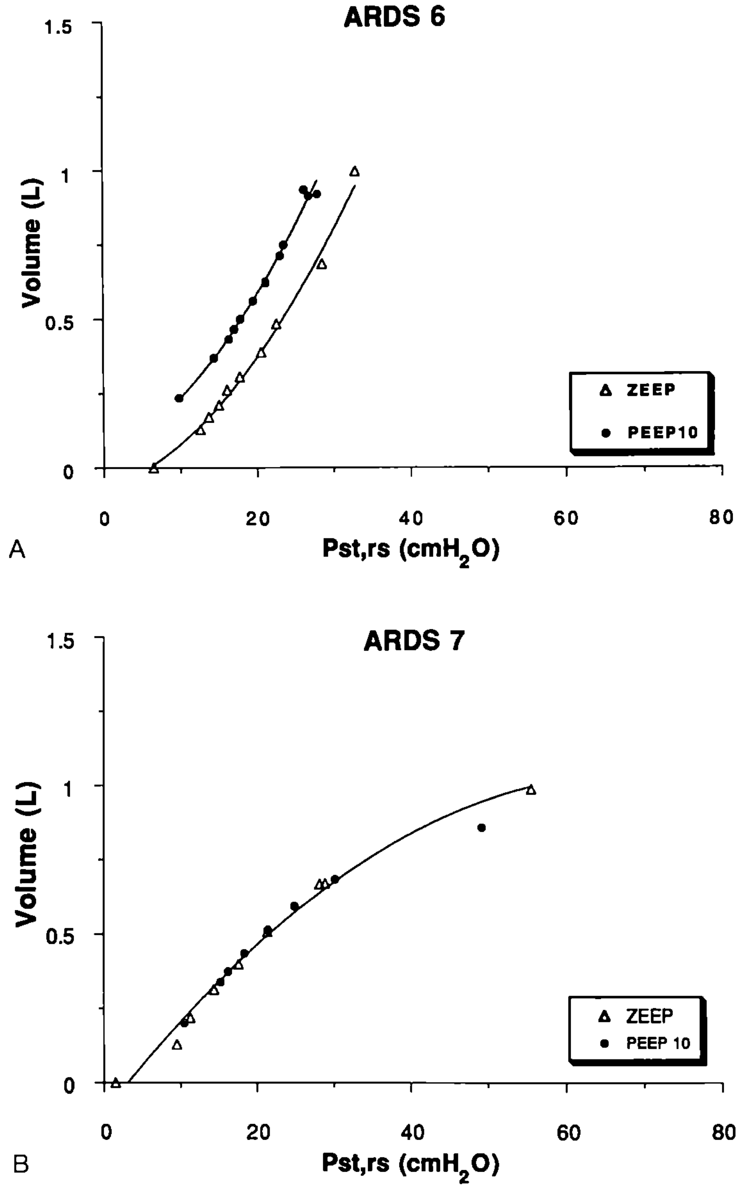

Figure 6. *A* and *B*, Static volume-pressure relationships obtained in two ARDS patients on ZEEP and on PEEP of 10 cm H_2O. Volume is expressed relative to end-expiratory lung volume on ZEEP. Pst,rs = static elastic recoil pressure of the respiratory system.

PEAK AIRWAY PRESSURE

Peak airway pressure (Pao,max) is the sum of the end-inspiratory Pst,rs, the pressure losses due to viscoelastic mechanisms or time-constant inequalities or both within the respiratory system, and the resistive pressure dissipations due to the resistance of the airways, endotracheal tube, and tubing connecting the patient to

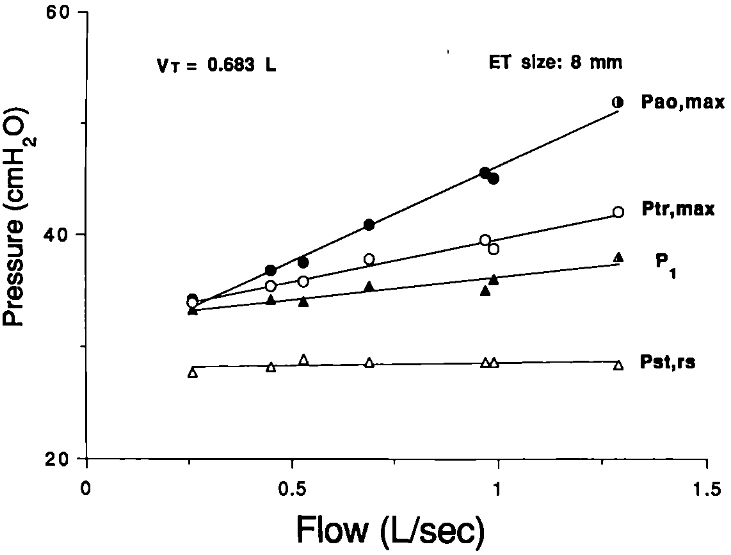

Figure 7. Relationship between peak airway pressure (Pao,max) and its components with flow in a sedated-paralyzed ARDS patient during constant-flow inflations with a fixed VT of 0.683 L delivered at the same end-expiratory lung volume but at different inspiratory flows. Ptr,max = peak tracheal pressure; P_1 = airway pressure immediately following end-inspiratory airway occlusion; Pst,rs = static elastic recoil pressure of the respiratory system.

the ventilator. Figure 7 illustrates the relationship between Pao,max and several of its components with flow in a patient with ARDS during constant-flow inflations with a fixed VT of 0.683 L delivered at the same end-expiratory lung volume but at different inspiratory flows. Ptr,max is the tracheal pressure measured 3 cm past the carinal end of the endotracheal tube. The end-inspiratory lung volume was fixed, as evidenced by the constancy of the end-inspiratory Pst,rs. By contrast, Pao,max increased markedly with increasing flow, reflecting, in part, the increase in resistive pressure due to the endotracheal tube (represented by the difference between Pao,max and Ptr,max). P_1 is the airway pressure immediately following end-inspiratory airway occlusion. The difference between Ptr,max and P_1 is the resistive pressure offered by the airways. The difference between P_1 and Pst,rs reflects the pressure losses due to viscoelastic mechanisms or time-constant inequalities or both within the respiratory system.[8, 19] Thus, it appears that under changing conditions of inspiratory flow, Pao, max is a poor parameter for monitoring. For instance, an increase in Pao, max could be due to a change in one or more of its components described previously: reduced compliance with a concomitant increase in Pst,rs; increased viscoelastic pressure dissipations or time-constant inequalities or both within the respiratory system with an increase in the difference between P_1 and Pst,rs; increased airway resistance with an increase in the difference between Ptr,max and P_1, and increased endotracheal tube resistance due to accumulations of bronchial secretions or tube kinking with an increase in the difference between Pao, max and Ptr, max. Therefore, to make a correct diagnosis, each component that can readily be obtained using the technique of rapid airway occlusion (see Fig. 4) should be examined. Nevertheless, in a given patient, the Pao,max is useful to observe if ventilator settings remained unchanged.

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Oxygenation and Blood Flow

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The basic principles of oxygenation were clearly enunciated by Joseph Barcroft in 1920.[8] The tripod supporting oxygen delivery necessitated the presence of sufficient oxygen transfer to blood in the lungs to produce a sufficient saturation of hemoglobin, a sufficient concentration of hemoglobin, and sufficient blood flow to carry the oxygenated hemoglobin to the tissues. In the 70 years that followed, it has not been possible to provide fully satisfying data for the optimal PaO_2, concentration of hemoglobin, or cardiac output in the critically ill patient.

This has not stopped a torrent of Delphic opinion based on insubstantial evidence and pontifical statement based on personal opinion. Fortunately, some recent studies, especially in patients with the acute phase of critical illness or injury, have indicated that survival can be improved markedly if patients are resuscitated to have survivors' oxygen transport parameters.[76] A supranormal cardiac output oxygen transport and uptake and blood volume seem to be of benefit. This explains the parallel realization that the stressed patient or patient compensating from a shock syndrome has a low oxygen extraction ratio as well as a raised metabolic rate. Normal parameters for a resting patient would inevitably lead to an oxygen debt in stress and sepsis and a toll of multisystem organ failure and death.

Oxygen transport to body tissues is the most pressing physiologic function of aerobic organisms. Tissue hypoxia is often encountered in critically ill patients. Understanding the factors that govern the process of tissue oxygen delivery ($\dot{D}O_2$) and utilization is essential in the management of hypoxic patients.[42]

TRANSPORT OF OXYGEN TO THE PERIPHERAL CAPILLARIES

Under basal conditions, the lungs take up 3 to 4 mL of O_2 per minute per kilogram of body weight and load most of it onto hemoglobin.[36] Ultimately, the total amount of O_2 passively diffused from the alveoli into the pulmonary capillary blood depends on the ventilation/perfusion relationship, the inspired O_2 concentration, and the chemical combination of oxygen with hemoglobin.[85]

Transport of oxygen toward the peripheral tissues is determined by the cardiac output ($\dot{Q}$) O_2 saturation, arterial oxygen tension (PaO_2), and hemoglobin concentration. This can be quantitated from the (indirect) Fick equation $\dot{D}O_2 = \dot{Q}(CaO_2)$ mL/02.min^{-1} where CaO_2 is the arterial oxygen content (mL/dL^{-1}).

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RELATIONSHIP OF OXYGEN AND HEMOGLOBIN

Because oxygen is poorly soluble in water, the amount normally dissolved in blood (0.00314 × PO_2 mL/dL^{-1}) is not sufficient to meet metabolic requirements. Comroe[26] calculated that if no hemoglobin was present, a resting man breathing room air would require a cardiac output of 83 L/min to carry enough oxygen to the tissues to support basal metabolic requirements. The total concentration of O_2 in blood is the sum of the oxygen dissolved in plasma and that bound to hemoglobin. The oxygen bound to hemoglobin can be calculated by noting that 4 moles of O_2 bind to 1 mole of hemoglobin.[9] Based on the precise determination of the molecular weight of hemoglobin, the O_2 binding capacity of 1 g is calculated to be 1.39 mL.[55] This amount is found to be too high in clinical practice. It is probably much closer to 1.31 mL.[61] The total oxygen carrying capacity of blood, which is approximately proportional to its hemoglobin concentration, is reduced by its conversion to methemoglobin and carboxyhemoglobin.[42]

The binding of O_2 to hemoglobin is a four-stage chemical process that results in the sigmoid-shaped oxyhemoglobin dissociation curve.[2] The advantage of the nonlinear O_2 binding characteristics of hemoglobin is that large changes in arterial PO_2 are effectively buffered so that arterial O_2 saturation remains close to 80% with a PO_2 as low as 40 mm Hg. The position of the oxyhemoglobin dissociation curve is usually described by the P50, which is the PO_2 at which the hemoglobin is 50% saturated with O_2. The standard value for P50 is 26.6 mm Hg.[1] The ability of hemoglobin to change its affinity for oxygen makes this molecule a very practical O_2 carrier. When $\dot{D}O_2$ becomes marginal, tissue oxygen utilization is enhanced by reduction in oxygen affinity. An increase in affinity is manifested by a shift to the left in the position of the oxyhemoglobin dissociation curve. Likewise, a shift of the oxyhemoglobin dissociation curve to the right signifies that the dissociation of O_2 is favored, resulting in greater amounts of O_2 released at a lower PO_2.[57] Changes in P50 are the result of molecular changes in the alpha-beta subunits produced by hydrogen ions (H^+), 2,3-diphosphoglycerate (2,3-DPG), and carbon dioxide.[73] Shifts in P50 are also influenced by temperature, by certain hemoglobinopathies, such as sickle cell disease,[15] or chronic hypoxic states.[37] Although a shift of the oxyhemoglobin dissociation curve position to the right enhances oxygen unloading in the tissues, the disadvantage is a loss of oxygen loading in the pulmonary capillary blood. When loading is accomplished at a low alveolar PO_2 (mm Hg), the oxygen loading loss produced by the right-shifted curve can exceed the unloading gain.[52] Some studies have indicated that at extremely low PaO_2, the body tends to shift the curve to the left.[56] This would enhance the oxygen loading at low alveolar PaO_2. In patients with a three-unit banked blood transfusion, Valtis and Kennedy[80] noted a defective gas transport function of stored red blood cells leading to an acute affinity hypoxia. These investigators reported a decreased arteriovenous oxygen content difference. They may have in fact been describing the reduced oxygen extraction ratio seen in stressed patients. However, as reported by Robin,[67] the acute limitations of an increased affinity of hemoglobin decreases with time because the initial 2,3-DPG-depleted red blood cells normalize glycolysis and replenish their intraerythrocytic 2,3-DPG content. In humans, transfusion with 2,3-DPG-depleted blood has shown no dramatic effects on tissue oxygenation.[7]

Although theoretical considerations suggest that alterations in O_2 affinity could be helpful in maintaining an adequate capillary PO_2 during O_2 unloading, in the normal individual, the position of the oxyhemoglobin dissociation curve seems to be a minor factor influencing body function.[16] In the care of the critically ill patient, despite much experimental evidence, changes in the hemoglobin affinity have not been demonstrated to have significant value.[16, 52]

HEMOGLOBIN CONCENTRATION AND HEMATOCRIT

As early as 1865, it was believed that quantities of red blood corpuscles were destroyed by ether.[70] Concern about the minimum hemoglobin requirement before surgery and anesthesia began in 1890. Miculicz[58] found that pulmonary edema occurred with hemoglobin levels below 20% of normal, therefore, he recommended that a hemoglobin of 30% of normal should be considered an absolute minimum before surgery could be performed safely.

After 1890, several publications promulgated a 10-g hemoglobin concept as the absolute requisite before surgery.[3, 24, 75] However, Cooley et al[25] demonstrated that patients could be managed successfully with hematocrits of 20% or lower during cardiopulmonary bypass. The assumption is that perfusion may actually be improved by the lowered hematocrit. In critically ill patients, however, hemodilution to this degree can compromise the delivery of O_2 to the peripheral tissues. Wilson and Walt[87] have shown that hematocrits of 38% or above are best related to survival in patients experiencing trauma or septic shock. Czer and Shoemaker[28] found that maximum survival rate occurred with pretransfusion hematocrit values from 27% to 33%. In addition, these studies demonstrated that oxygen availability significantly increases after transfusion when pretransfusion values are below 33%. Patients with end-stage renal disease frequently have a successful surgical outcome with a hemoglobin of less than 7 g.[5] Mortality rates can approach 87% in patients undergoing surgery with a mean hemoglobin of 3 g.[40] Patients with cardiac or coronary artery disease also have increased morbidity with anemia. Richardson and Guyton[66] have demonstrated experimentally that the optimum $\dot{D}O_2$ for the least myocardial oxygen consumption occurs when the hematocrit is in the 40% to 45% range. As the hematocrit rises further, the incidence of vascular occlusive episodes increases.[62] Exercise performance and $\dot{V}O_2$ max improve with hemoglobin levels greater than 16 g.[88] From the previous discussion it is evident that the optimal hematocrit value that provides optimal O_2 delivery is not fixed and may not necessarily be normal at 45%.

Apparently some organs can respond better to both increases and decreases in hematocrit. During anemia, compensatory increases in cardiac output may necessitate redistribution of blood flow to areas of high demand. Coronary and cerebral blood flow increase in association with regional vasodilation.[27] The reactions of the body to anemia tend to direct the delivery of oxygen to maintain supply-dependent tissues, while other circulatory beds, such as the splanchnic, kidney, and skin vasculature, which are supply independent, operate with a reduced supply. Because most of the oxygen available is extracted by supply-dependent tissues, even under basal conditions, to avoid anaerobic metabolism, any increase in cardiac work must therefore be accompanied by an increase in coronary blood flow. The increase in myocardial blood flow is secondary to increased demands. As demonstrated by Cain,[20] during the production of anemic hypoxia in dogs with isovolemic dextran hemodilution, extra oxygen use by the heart accounts for the increase in total oxygen uptake. The capacity of the coronary circulation for further blood flow is exhausted at a hematocrit near 10% in dogs.[82] Below that value, insufficient oxygen supply to the myocardium limits the circulatory adaptation to normovolemic hemodilution at rest.

Cerebral blood flow also increases during anemia. This has been demonstrated in both animals and man.[83] At hematocrits less than 30%, increased perfusion is associated with cerebral vasodilatation but also can be augmented by decreased viscosity.[14] Blood flow to supply-dependent organs is reduced due to the relative vasoconstriction that occurs in some tissues during acute anemia.[35] When the cardiovascular adaptive reserve is exhausted as hematocrit is decreased, the total body blood flow falls; however, whole body oxygen consumption is maintained to a hematocrit of less than 10% by an increase in systemic oxygen extraction ratio.[22] Wilkerson et al[86] demonstrated a linear increased in oxygen extraction ratio as the hematocrit diminished until a critical point at 10%, when an oxygen extraction ratio of 50% was attained. Beyond this point, experiments in both rats and dogs have shown that baseline O_2 consumption is no longer maintained, leading to metabolic acidosis, hemodynamic instability, and eventual death.[4]

HYPOXIA AND ARTERIAL OXYGEN TENSION

The original classification of anoxemia by Barcroft[8] in 1920 is still in use today. He categorized anoxemias as hypoxic, anemic, or stagnant. Oxygen transport requires adequate oxygenation of the blood, sufficient hemoglobin, and adequate cardiac output. Later, Peters and Van Slyke[63] described histotoxic anoxia, a condition in which the cell cannot use the oxygen delivered; cyanide poisoning is given as a prime example. Currently, theories center around distributional phenomena, as seen in septic shock, to explain the inability of the cells to utilize the O_2 that is being delivered.[77] Hypoxia is a condition often encountered in critically ill patients due to a reduction in arterial oxygen tension, hemoglobin, cardiac output, or altered tissue perfusion. It also can occur in normal subjects at high altitudes. At an altitude of 8838 meters (Mt. Everest), the calculated arterial oxygen tension is 29 mm Hg.[84] This low arterial PO_2 can be tolerated by some healthy persons by respiratory and circulatory adjustments; however, in the critically ill patient, evidence of tissue hypoxia is seen with less severe reduction in PaO_2. Furthermore, a limitation in oxygen utilization has been reported in several conditions in which systemic oxygen delivery is well above the normal range.[6, 21, 29, 44, 60]

The critical level of PO_2 required for oxidative phosphorylation is uncertain. In the isolated mitochondria, there is no significant decrease in the respiration as measured by the oxidation of cytochrome C until the PO_2 in the perfusion media falls below 0.5 mm Hg.[50] Because the oxygen affinity of this enzyme is high, it would appear to indicate that severe reductions in oxygen delivery are necessary before impairment of ATP synthesis occurs.[67] On the other hand, several oxygen-dependent extramitochondrial processes have a relative lower affinity for oxygen. It is therefore reasonable to consider that with moderate oxygen depletion, the evidence of tissue hypoxia that is frequently seen in critically ill patients could at times be due to the failure of these extramitochondrial oxygen-requiring reactions rather than to deficits in the ATP-producing mitochondrial oxidase systems. In addition, it has been proposed that moderate reductions in PO_2 would interfere with the extramitochondrial synthesis of norepinephrine, epinephrine, and other neurotransmitters, such as serotonin, which may be necessary for survival under the stressful conditions of critical illness.[32, 68]

CARDIOVASCULAR ADJUSTMENTS TO HYPOXIA

Adaptations to acute hypoxemia include a series of autonomic and autoregulatory adjustments throughout the body in an attempt to protect the supply-dependent organs (brain, heart) by diverting blood flow away from supply-independent organs (skin, splanchnic region, kidneys, muscle).[18] Cerebral function remains intact until the PaO_2 falls below mm Hg, at which point vasodilation occurs, increasing the cerebral blood flow to 150% of normal flow.[72] Adenosine may be an important mediator in this process. Cerebral spinal pH may rise as a result of hyperventilation opposing or even preventing the cerebral vasodilatation.[71]

Coronary vessels respond to hypoxemia by vasodilatation.[10] Hypoxia is considered to be the most potent physiologic stimulus in evoking relaxation of coronary vessels. The mechanism whereby a low PO_2 can cause vasodilatation is not clear. An increase in cardiac output also occurs as a compensatory adjustment to hypoxemia; this is mainly related to an increase in stroke volume. However, a moderate increase in heart rate can be seen as a result of a reduction in the vagal tone due to the stimulation of pulmonary stretch receptors by hyperventilation.[69]

Relative to the marked vasodilation in cerebral and coronary vessels, the renal circulation remains unchanged, even with PO_2 as low as 35 mm Hg.[23] At this level of PO_2, plasma renin activity does not increase in man, indicating that sympathetic nervous system activity to the kidney does not increase.

Stimulation of peripheral chemoreceptors by low arterial PO_2 produces marked reflex vasoconstriction in skeletal muscle and some vasodilation in the cutaneous bed.[46]

The pulmonary vasoconstriction response to hypoxia is well known but poorly understood. Alveolar PO_2 regulates adjacent vascular tone. In systemic hypoxemia, widespread pulmonary vasoconstriction redistributes blood flow to the upper portions of the lung, thereby improving ventilation/perfusion.[41]

DETERMINANTS OF OXYGEN TRANSFER TO THE CELL

In the capillaries, oxygen dissociates from oxyhemoglobin and diffuses into the tissues.[53] The diffusion of oxygen into the cells depends on the distance and the driving pressure gradient between the capillaries and the mitochondria.[30, 34] Because the intramitochondrial PO_2 is close to zero, the diffusion gradient driving oxygen into the mitochondria is essentially equal to the capillary PO_2. Diffusion is also determined by the surface area for diffusion.[54] Capillary recruitment, a mechanism by which the microvascular bed responds to increases in metabolic demands, can improve the diffusion of oxygen by increasing the available surface area.[48] In dog gracilis muscle, the density of available capillaries increases from approximately 40% at rest[13] in response to demands such as exercise or hypoxia, thereby shortening diffusion distance. Direct observation of capillary networks has not universally confirmed the concept of capillary recruitment. Hrdlicka et al[49] found that most capillaries are perfused at rest, which supports the concept that the pressure gradient is the critical factor in tissue oxygenation rather than the shortening of diffusion distance by capillary recruitment.

The capillary PO_2 is commonly calculated based on the modified Krogh tissue cylinder model, which takes into account a progressive fall in this pressure as oxygen is removed along the length of the capillary.[38, 51, 53, 78] Assuming a constant oxygen uptake, the fall in saturation is linear, and because of the shape of the oxyhemoglobin dissociation curve, the fall in PO_2 is nonlinear and reaches its lowest point at the venous end of the capillary, which is sometimes assumed to be an approximation of mean tissue PO_2.[43]

In addition to capillary recruitment and pressure gradient, other factors that influence the ability to maintain an adequate oxygenation at the tissue level are capillary hematocrit and flow. Increases in capillary flow in the hyperdynamic states of sepsis or anemia can interfere with oxygen release from erythrocytes by not providing enough time for oxygen release.

The Kroghian concept of capillary oxygen exchange has been challenged recently. Due to the close proximity between arterioles and venules, arteriovenous diffusional oxygen shunting has been proposed by Piiper et al[64] in a countercurrent model of capillary oxygen exchange. In this model, because the venous PO_2 is higher than in the Kroghian model, tissue PO_2 may be overestimated. Based on kinetics of oxygen release from hemoglobin, the time required for oxygen to be dissociated will result in a capillary PO_2 that is significantly lower than predicted, assuming instantaneous release. Therefore, the venous PO_2 will not accurately measure the end capillary and tissue PO_2 as proposed in the Kroghian model.[44]

OXYGEN TRANSPORT AND UTILIZATION

The classic view of the normal relationship between oxygen consumption and O_2 transport is that $\dot{V}O_2$ is a reflection of metabolic demands, and that over a wide range of changes in $\dot{D}O_2$, $\dot{V}O_2$ is not affected.[30, 79] Cain[19] demonstrated that as $\dot{D}O_2$ was reduced progressively, a level was reached below which $\dot{V}O_2$ declined lineraly with further decreases in $\dot{D}O_2$. The level of $\dot{D}O_2$ at which the $\dot{V}O_2$ becomes dependent on the supply of O_2 is the *critical $\dot{D}O_2$*. In anesthetized dogs, the critical value was the same regardless of whether total O_2 delivery was reduced by anemia or hypoxia.[19]

Under normal conditions of O_2 supply, the $\dot{V}O_2$ is independent of $\dot{D}O_2$, but with reductions to approximately 10 mL/minute/kg, the $\dot{V}O_2$ eventually becomes supply dependent. Below this critical $\dot{D}O_2$, because O_2 demands are no longer satisfied, a lactic acidosis develops, reflecting the onset of anaerobic metabolism.[31]

In anesthetized patients with coronary artery disease, Shibutani and associates[74] found that above a total O_2 transport rate of 8.2 mL/kg/min, O_2 uptake was independent of supply.

Recent studies in critically ill patients have challenged this classic view. Several studies revealed that $\dot{V}O_2$ appeared to be limited by O_2 transport even at normally adequate levels of $\dot{D}O_2$, and a critical $\dot{D}O_2$ could not be identified in the majority of patients. This linear relationship has been termed pathological supply dependency.[6, 11, 21, 29, 44, 50, 59]

Clinical and laboratory studies suggest that there is a positive correlation between $\dot{V}O_2$ and survival.[76, 79, 81] Because the $\dot{V}O_2$ is dependent on $\dot{D}O_2$, it is reasonable to assume that increasing $\dot{D}O_2$ even to supranormal values could be one of the major physiologic goals of therapy. An increase in $\dot{D}O_2$ can be achieved by various approaches, including volume expansion, blood transfusion, and inotropic drugs. Gilbert et al[39] showed that both fluid loading and transfusion-related increases in $\dot{D}O_2$ led to an increase in $\dot{V}O_2$ in the presence of lactic acidosis, a marker of anaerobic metabolism. Cathecholamines, on the other hand, induce increases in $\dot{V}O_2$, even in patients with normal lactate levels. Cathecholamines can exert a direct effect on oxidative metabolism that does not depend on oxygen debt.[12, 39]

Recent studies have shown that infusion of prostacyclin, but not of phentolamine, significantly increases $\dot{V}O_2$, unmasking an oxygen debt that frequently occurs in critically ill patients despite apparent adequate O_2 transport. The differences between these two vasodilators are thought to be related to the preferential effect on the microcirculation by the prostacyclin, thereby improving the distribution of microcirculation flow in sepsis.[65]

CONCLUSIONS

The best parameters for oxygen transport and blood flow are hard to define. This is probably because of individual patient requirements. In the acute phase of critical illness or injury, meeting the needs of supply-dependent oxygen uptake has been shown to improve the prognosis. Published justification can be found for a PaO_2 from 70 to 200 mm Hg, a hematocrit of 27% to 44%, and a cardiac output that indexes above the calculated resting normal for the patient. The answer to the controversies surrounding these enormous ranges is to titrate the patient's therapy to goals consistent with survival both in terms of avoiding oxygen debt and maintaining organ function. The argument about specific numbers for the parameters that achieve these goals then becomes moot.[65]

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Vasodilating Drugs and Regional Circulation

Focus on Pulmonary Vasculature

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The pulmonary circulation is a low-pressure, high-flow, low-resistance vascular system. It is capable of accepting the entire cardiac output at a pulmonary artery pressure (PAP) of only 15 mm Hg. The major function of the lungs is gas exchange, and in the past the pulmonary circulation has frequently been considered a passive conduit for blood flow through the lungs. However, during the last two last decades, the view of the pulmonary circulation has evolved to include concepts such as the effects of the pulmonary circulation on right and left ventricular function, the active regulation of global and regional pulmonary vascular resistance, the role of the pulmonary circulation in the prevention of regional lung ischemia, the effect of alterations in the longitudinal distribution of pulmonary vascular resistance on the development of pulmonary edema, and the metabolic functions of the lungs.

Vasodilating agents are commonly used in critically ill patients to decrease afterload, increase cardiac output, and improve cardiac function. Many of these patients have a wide range of abnormal ventilation-to-perfusion relationships because of underlying chronic lung disease, adult respiratory distress syndrome (ARDS), or pneumonia. Pulmonary vasodilators affect perfusion, and, thus, a vasodilator-induced hypoxemia is predictable with the use of some of these drugs. Regional changes in pulmonary vascular resistance are particularly important because they can alter the relative distribution of blood flow within the lung, leading to altered ventilation-perfusion relationships and accompanying changes in gas exchange. This article outlines the vasomotor regulation of the pulmonary circulation and discusses aspects of the use of specific pulmonary vasodilating agents.

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DETERMINANTS OF PULMONARY VASCULAR RESISTANCE

Unlike the systemic circulation, the pulmonary vessels are designed as a low-pressure, low-resistance system. The walls of the pulmonary artery and its branches and arterioles are much thinner and contain less smooth muscle and elastin than that found in their counterparts in the systemic circulation. The pulmonary vessels therefore do not have the same capacity for vasoconstriction. Whereas the systemic capillaries are usually arranged as a network of tubular vessels with some interconnections, the pulmonary capillaries are sandwiched between adjacent alveoli in such a manner that the blood flows as if in thin sheets. This provides a large surface area (126 m^2) for maximal exposure of the capillary blood to the alveolar gases. Only a thin layer (1.2–1.6 μm) of vascular endothelium and alveolar epithelium with their basement membranes and intestinal space separate the blood and alveolar gas. The very large metabolically active endothelial surface is now recognized as the site of many of the metabolic and pharmacokinetic functions of the lung. Several circulating hormones with diverse pharmacologic functions, including biogenic amines, prostaglandins, and peptides, are modified during passage through the lungs.[29, 34, 108]

Pulmonary Vascular Resistance

Pulmonary vascular resistance (PVR) is a measure of the hindrance offered by the pulmonary vascular bed to the flow of blood through it. The ratio of pulmonary vascular resistance to that in the systemic vascular bed is approximately 1:6. Alterations in pulmonary vascular tone may change total or regional PVR, thereby affecting right (and therefore left) ventricular output and the matching of ventilation to perfusion. PVR is equally divided between arteries, capillaries, and veins. More than half of the total resistance lies in the pulmonary microcirculation, i.e., in vessels without muscular walls.

Traditionally, hemodynamic studies of the pulmonary circulation are based on the Poiseuille relationship, which defines vascular resistance in terms of mean pressure and flow. The calculation for the pulmonary circulation is $PVR = P/Q$, where P is the pressure drop across the pulmonary circuit and Q is pulmonary blood flow (cardiac output). P is generally calculated as PAP (mean) − PCWP (or LAP), where *PCWP* is the pulmonary capillary wedge pressure and *LAP* is the left atrial pressure.

Pulmonary vascular resistance can be altered by several mechanisms. Passive changes in the diameter of the pulmonary blood vessels can be induced by increased cardiac output or by elevations of left atrial pressure or both. One familiar source of difficulties in interpreting a change in calculated pulmonary resistance occurs when pulmonary pressures or blood flow or both change concurrently. This makes it difficult to decide how much of the change in resistance is a passive consequence of the change in pressure or flow, per se, and how much is caused by active alteration in pulmonary vascular tone. These considerations are important in view of the current interest in using pulmonary vasodilator agents. Care must be taken when attributing a decrease in calculated PVR to vasodilation unless PAP, left atrial pressure, and cardiac output remain unchanged.

Pulmonary vascular resistance has generally been considered to decrease with increasing cardiac output as a result of the distension of already patent vessels and recruitment of previously nonperfused vessels. However, more recent data using pressure-flow curves demonstrate a linear increase in pressure and flow. The pressure intercept corresponding to zero flow is referred to as the opening pressure. When this pressure exceeds left atrial pressure, calculated PVR will decrease when cardiac output increases even though pulmonary vascular tone has not changed.

The concept of vascular impedance extends that of resistance with use of the relationship between the pulsatile pressure and pulsatile flow. Vascular impedance is calculated as the ratio of corresponding frequency components in the arterial pressure and flow waves. Although the determination of pulmonary vascular impedance is considerably more complicated than that of resistance, it does afford the opportunity for additional insights into various aspects of pulmonary circulation.[28]

Vasomotor Regulation

Although changes in pulmonary resistance are achieved mainly by passive factors, resistance can be modified actively by neural, chemical, and humoral influences on the pulmonary vascular bed. The vascular endothelium is active in removal, biosynthesis, and release of several vasoactive substances that can have significant effects on pulmonary vascular tone as well as on systemic circulation. However, the contribution of local hormones released and destroyed within the lungs to the setting of pulmonary vascular tone is difficult to uncover. For example, vasoactive prostaglandins can have a half-life too short for their detection in systemic arterial or even in pulmonary venous blood. Also, it is not possible to distinguish between the effects of locally released catecholamines and those brought to the pulmonary vessels from the systemic circulation.[69]

The vasomotor tone of normal pulmonary circulation in the adult has been found to be in a state near maximal dilatation.[63, 86] Initial tone is higher in the fetus[23] and in the native residents of high-altitude geographic areas.[76] Whether tone increases during exercise as mixed venous pressure of O_2 decreases is unknown.[28] Vasodilator prostaglandins are important to the low initial tone of the pulmonary circulation under natural or near-natural circumstances.[10, 61]

Many mediators can cause either dilation or constriction of the pulmonary vessels depending on the dose, administration rate, and route of administration of the mediator and on the species, age, sex, health, and extent of experimental manipulation of the test subject. Another important factor is the preexisting level of pulmonary vascular tone. In experimental studies, the initial tone in pulmonary vessels can be increased by a variety of influences; catecholamines might predominate in some circumstances, and in others, angiotensin,[10] serotonin,[11] vasoconstrictor prostaglandins,[33] or mysterious plasma factors may predominate.[12] As a rule, pulmonary resistance vessels that manifest high initial tone show a blunted response to pulmonary vasoconstrictors. Conversely, when initial tone is high, the effects of vasodilators are more impressive.[3] When initial tone is high, as during combined hypoxia and acidosis, stimulation of the β-receptor adrenergic system and the infusion of acetylcholine give an impressive vasodilatation, whereas neither has much effect on normal pulmonary circulation.[41] It also is apparent that although the pulmonary vascular response to some mediators is due to direct actions on the smooth muscle, the response to others is either mediated or modulated by the release of one or more secondary substances (e.g., eicosanoids, histamine) from sources such as endothelium and mast cells. To obtain a thorough understanding of the role and mechanism of action of pulmonary vasoactive agents, a range of doses of the substance must be studied under conditions of normal and increased vascular tone with and without inhibitors of the activity of suspected secondary mediators or modulators.

Nervous Control

The pulmonary blood vessels are innervated by sympathetic fibers but more sparsely than systemic vessels. Unlike most systemic vessels, the pulmonary blood vessels receive some parasympathetic innervation. In unstressed individuals, there is no evidence to suggest involvement of the autonomic nervous system of the lungs in the regulation of the pulmonary circulation.[85] Vagal stimulation dilates the pulmonary vasculature.[68] The sympathetic innervation includes α- and β- adrenergic receptors. The α-adrenergic receptors constrict, whereas the β-adrenergic receptors dilate. Norepinephrine, an α-adrenergic agonist, evokes pulmonary vasoconstriction, whereas isoproterenol, a β-adrenergic agonist, causes vasodilatation.[87, 92] Epinephrine, which is both an α- and a β-agonist, elicits pulmonary vasoconstriction or vasodilation depending on the experimental circumstances.[7] The α-adrenergic receptors appear to predominate both numerically and functionally under natural conditions at rest.[79] However, under natural conditions, the sympathetic nervous system contributes little to pulmonary vascular tone[28]; its influence may be increased greatly under stressful conditions. The walls of the pulmonary arterial tree stiffen during sympathetic nervous stimulation, thereby increasing the pulsaltiveness. This may improve perfusion of underperfused or nonperfused portions of the lungs.[47, 56] These functional connections between the central nervous system and the adrenergic nervous system with the pulmonary circulation provide a mechanism by which the pulmonary circulation can quickly engage in the circulatory adjustments that accompany a fight-or-flight reaction, thus, helping to match alveolar blood flow to alveolar ventilation.[22, 28]

Studies have established the existence of extrapulmonary reflexes from the aortic and carotid chemoreceptors as well as from baroreceptors in evoking pulmonary vasoconstriction.[101] However, the extent to which these reflexes are operative under natural conditions is not clear.

Chemical Control

Within the lung, blood interacts with the very large metabolically active endothelial surface that is now recognized as the site of removal, biosynthesis, and release of several vasoactive endogenous substances that have effects on pulmonary as well as on systemic circulation.[34, 49] Thus, aortic blood can differ markedly from central venous blood in its concentration of substances that have profound effects on circulation, including vasoactive amines, prostaglandins, and peptides.[28] Some of these substances evoke pulmonary vasoconstriction whereas other evoke vasodilation.

Vasoactive Amines. Norepinephrine and serotonin (5-HT) both elicit pulmonary vasoconstriction. Both of these amines are almost completely removed and deaminated in the endothelial cells of the pulmonary circulation. The removal of these biogenic amines occurs rapidly; their concentration in pulmonary arterial blood can be reduced effectively in a single transpulmonary passage.[34] Because the endothelial cells cannot account alone for the rapid removal, other processes, such as uptake into platelets, adrenergic nerve endings, and neuroepithelial cells, are important for pulmonary retention of the biogenic amines.[35] Serotonin and norepinephrine are found in the lung, and, thus, de novo biosynthesis of these amines by the lung seems probable.[89] The adrenergic innervation of the lung suggests that neuronal regulation of the lungs' metabolic functions is possible.[34]

Changes in the endothelial metabolism of serotonin and norepinephrine in the lung during disease have been linked to alteration in cardiovascular regulation. Systemic hypertension after cardiopulmonary bypass has been linked to increased circulating concentrations of norepinephrine.[78, 110] Patients with pulmonary hypertension have been found to have no net transpulmonary norepinephrine gradient.[34, 97]

Eicosanoids and Their Precursors. The eicosanoids include the prostaglandins (PG), the thromboxanes, and the leukotrienes. They are metabolized either via the cyclooxygenase or lipooxygenase pathway. The eicosanoids have variable effects on the pulmonary circulation. Certain metabolic products of the cyclooxygenase pathway have been found to act as pulmonary vasoconstrictors, e.g., $PGF_{2\alpha}$, PGE_2, and thromboxane A_2, whereas others are pulmonary vasodilators, e.g., PGE_1 and prostacyclin. Leukotrienes, generated by the lipooxygenase pathway, are potent pulmonary vasoconstrictors.

A balance between prostaglandin vasodilator activity and the constrictor effect of thromboxane A_2 and leukotrienes is suspected to be of considerable importance in setting the low initial tone of normal pulmonary circulation.[33, 40, 50] The lungs have an important role in synthesizing and inactivation of highly vasoactive eicosanoids. This metabolic activity is important for the regulation of pulmonary vascular tone as well as for extrapulmonary effects because of the lungs' position in the vascular system. It is difficult to predict the effects of eicosanoids on pulmonary circulation; either the cyclooxygenase or lipooxygenase pathway may predominate dependent on the experimental setting, fatty acid profile of the cell membrane phospholipids and blood, or concomitant medication.

Peptides. Bradykinin is inactivated in the lungs by the same converting enzyme that converts angiotensin I to angiotensin II. Bradykinin is consistently a powerful systemic vasodilator. It also usually evokes pulmonary vasodilation, but this effect is not as predictable as its systemic response. The pulmonary vasodilator effect is much more consistent and striking in the lungs of the fetus and newborn than in the adult.[15] The biologic role of bradykinin in regulating the pulmonary circulation is unclear.[28]

Angiotensin II, formed in the lung from angiotensin I, generally but not invariably elicits pulmonary vasoconstriction.[7] Small doses administered intravenously increase PAP without discernible effect on the systemic circulation.[41] An estimated 90% of circulating angiotensin I is converted to angiotensin II in the pulmonary vascular bed. Angiotensin II is not metabolized by the lung, which is consistent with its role as a "circulating" hormone.[108]

Histamine has been found to elicit variable responses on pulmonary circulation.[90] Most studies suggest that histamine is a powerful vasoconstrictor and a systemic vasodilator. The combination of pulmonary pressor effect and the location of histamine in pulmonary mast cells adjacent to muscular pulmonary arteries raised the suspicion that histamine acts as an important local mediator in the regulation of pulmonary circulation.[42] However, other studies have failed to support this.[109] The identification of H_1 and H_2 receptors and the use of blocking agents have suggested that pulmonary vasoconstriction is mediated by H_1 receptors and vasodilatation by H_2 receptors.[3, 28]

Hypoxic Pulmonary Vasoconstriction. Hypoxic pulmonary vasoconstriction describes a mechanism by which an increase in PVR develops in lung areas with tissue hypoxia. This causes a shift of blood flow away from the hypoxic area to better aerated lung segments and thereby leads to improved gas exchange by decreasing blood flow to the nonventilated lung.[109] In normal lungs, the hypoxic pulmonary vasoconstriction response seems to be maximal when P_AO_2 is approximately four kPa.[64] Acidosis also is a pulmonary constrictor. The mediator of the hypoxic pulmonary vasoconstriction response has not been identified.[5] Pharmacologic agents that interfere with this protective mechanism decrease arterial PO_2 and increase shunting. Thus, many of the vasodilating and anesthetic agents influence the hypoxic pulmonary vasoconstriction response; this is discussed in the next section.

PULMONARY VASOACTIVE AGENTS

Vasodilator therapy is an accepted method of treatment for patients with systemic hypertension or left ventricular failure. Clinical interest in specific pulmonary vasodilator agents in the treatment of acute right heart failure, ARDS, and pulmonary hypertension has increased. Over the last decades, many agents have been evaluated as pulmonary vasodilators. Most agents have been evaluated as pulmonary vasodilators because they are known to be potent systemic arterial dilators. This systemic vasodilation can occur at doses that have no effect on pulmonary vascular resistance, and the major problem with pharmacologic therapy has been systemic hypotension due to the potent systemic arterial dilating effects of these drugs. These agents have been effective in selected patients; however, frequent treatment failures and major adverse effects, including systemic hypotension and vasodilator-induced hypoxemia, have occurred. An ideal pulmonary vasodilator for the treatment of pulmonary hypertension and associated right ventricular dysfunction would decrease PAP, increase cardiac output, and not worsen systemic blood pressure or pulmonary-perfusion matching. A drug with preferential pulmonary (versus systemic) vasodilator effects minimizes the risk of systemic hypotension.

The major determinant of PaO_2 and $PaCO_2$ is the matching of ventilation to perfusion. Average normal ventilation (V) is 6 L/min, which equals the normal cardiac output (Q) of 6 L/min for an overall V/Q of 1. Regional variations in V/Q exist within the lung itself, being high at the lung apices ($V/Q > 1$) and lower ($V/Q < 1$) at the bases. Imbalance in the V/Q is the most common cause of impaired oxygen and CO_2 transfer and is the major cause of hypoxemia in patients with chronic obstructive pulmonary disease (COPD), ARDS, and pneumonia. Hypoxia-induced pulmonary vasoconstriction is the primary physiologic response for restoring V/Q to normal; however, this vasoconstriction can be so intense and widespread that pulmonary hypertension occurs. To understand the effects of vasodilators on oxygenation, the direct action of the specific drugs on the pulmonary arterial and venous beds as well as their effect on cardiac contractility, cardiac output, intrapulmonary shunts, and the ratio of systemic to pulmonary blood volume must be considered. Thus, rational drug selection for clinical application depends on baseline hemodynamic parameters.

Nitrates

Nitrates are direct-acting vasodilators that alter pulmonary hemodynamics in a complex manner. Their pulmonary vasodilating responses are dependent on the existing level of vasomotor tone in the pulmonary vascular bed. The response is minimal under normal conditions but enhanced when vascular tone is increased.[51] The vasodilator action is independent of passive factors, such as changes in pulmonary blood flow or left atrial pressure, and is not secondary to the effect of these agents on the systemic circulation.[51] The nitrates have been found to reverse hypoxic pulmonary vasoconstriction.[40, 66] A portion of the decrease in PVR observed when nitrates are administered is probably due to the reversal of hypoxic vasoconstriction, leading blood to poorly ventilated lung units as evidenced by a decrease in PaO_2 during infusion. The effects on arterial oxygenation depend on the degree to which pulmonary vasoconstriction is maintaining arterial oxygenation. The potential for adverse hemodynamic effects and deterioration of gas exchange when nitrates are administered necessitates that they are used with caution in the management of the patients with pulmonary conditions.

Nitroglycerin is a systemic arterial dilator, a systemic venodilator, and a pulmonary arterial dilator.[44] It has been found to have a major pulmonary vasodilator effect, and several studies in experimental models and in patients with pulmonary hypertension suggest that nitroglycerin is a pulmonary vasodilator at doses that do not decrease systemic blood pressure below acceptable levels.[18, 60, 66]

Sodium nitroprusside is more potent than nitroglycerin as a systemic arterial vasodilator. In contrast, sodium nitroprusside has been found to affect PVR only to a minor degree in experimental animals with lung damage.[43, 74, 80] Clinical studies also suggest that sodium nitroprusside affects PVR only at doses that affect systemic vascular resistance.[17, 55, 77] The different hemodynamic patterns seen with nitroglycerin and sodium nitroprusside are best explained by their relative potencies as pulmonary and systemic vasodilators. Sodium nitroprusside can be distinguished from nitroglycerin, which has been found to induce parallel decreases in PVR and systemic vascular resistance in that it has resulted in systemic hypotension at doses that did not alter PVR and PAP.[74]

Nitrates have been investigated in experimental ARDS models.[4, 21, 75] Benoit et al[4] reported that nitroglycerin produced a 26% decrease in cardiac output when administered to dogs with oleic acid pulmonary edema. In contrast, Pearl et al[75] reported a 40% increase in cardiac output in a similar model. In the latter study, however, the investigators gave a higher dose of oleic acid to the dogs, which resulted in a 46% increase in PAP and a 155% increase in PVR; the protocol used by Benoit et al produced only a 18% increase in PAP and a 78% increase in PVR. These differences in baseline status may explain the different effects on cardiac output.[73] When baseline PAP and PVR are very high, cardiac output is limited by right rather than left ventricular performance, so that pulmonary vasodilation can reduce right ventricular afterload and result in an increase in cardiac output. If the PAP and PVR are moderately elevated, the predominant effect of nitroglycerin is systemic vasodilation with a corresponding decrease in left ventricular preload and cardiac output. Thus, the effects of a nitroglycerin infusion in acute respiratory failure will be a function of baseline volume status, systemic and pulmonary vascular tone, right and left heart function, and the dose given. When nitroglycerin is administered to patients with ARDS in whom cardiac output is not limited by PVR, the result is arterial hypoxemia, and, if the patient is hypovolemic, decreased cardiac output and hypotension may occur. In contrast, when nitroglycerin is administered to patients with severe pulmonary hypertension in whom cardiac output is limited by right heart afterload, an increase in cardiac output may occur.[75] The effects on arterial oxygenation will depend on the degree to which hypoxic pulmonary vasoconstriction was maintaining arterial oxygenation. The potential for adverse hemodynamic effects and deterioration of gas exchange when nitroglycerin is administered in these animal models of acute lung injury indicate that caution should be exercised in the use of nitroglycerin in humans with ARDS. Zapol et al[115] infused nitroprusside for short periods in patients with early-stage ARDS. They reported a 38% increase in cardiac output, whereas mean PAP and pulmonary capillary wedge pressure decreased. The venous admixture increased from 23 to 32%. It was hypothesized that the nitroprusside infusion in early-stage ARDS produced pulmonary vasodilation, particularly in areas of lung injury, permitting cardiac output to increase at a lower PAP.[111] Nitroprusside infusions in patients with severe- and late-stage ARDS did not reduce the PAP or PVR.[115]

Hydralazine

Hydralazine decreases blood pressure by a direct systemic vasodilator effect on the arterioles, the reduction being associated with an increase in cardiac output and heart rate. The cardiac effects have been attributed to a reflex activation of the cardiac sympathetic nerves secondary to the decrease in systemic blood pressure. However, some investigators have suggested that hydralazine has an additional direct stimulating effect on the myocardium.[53]

Hydralazine has been used in several studies of patients with pulmonary hypertension. Although initial reports suggested beneficial effects,[62, 88] more recent studies reveal short- and long-term deleterious effects.[57, 70] Careful scrutiny of the early studies shows that the reduction in PVR rarely exceeded the reduction in systemic resistance, suggesting that the major effect of hydralazine was seen in the systemic circulation.[32] The decrease in PVR is probably related to the increased cardiac output caused by the reduction in SVR and not a direct effect on pulmonary vessels.[82]

The deleterious effects of hydralazine therapy have been documented in patients with pulmonary hypertension.[57, 70] Packer et al[70] found that hydralazine decreased SVR by 40% but PVR by only 21%. Stroke volume and PAP were unchanged. Four of thirteen patients experienced hypotensive episodes; progressive renal insufficiency developed in one patient and another died. The decrease in SVR with a reflex increase in heart rate and cardiac output could precipitate myocardial decompensation in clinical use. These findings indicate that extreme caution must be used when the efficacy of hydralazine is tested in patients with pulmonary hypertension, in view of the potential for sudden cardiovascular catastrophe.

Calcium Channel Blocking Agents

Calcium channel blockers are generally safe and well tolerated in patients with several types of cardiovascular disorders. They combine vasodilator and negative inotropic and chronotropic properties. However, all calcium channel blockers are not equivalent. Some calcium antagonists have mainly peripheral vascular action (e.g., nifedipine), others have the same action on heart and periphery (e.g., verapamil), and still others have a range of action that lies in between (e.g., diltiazem).[32] This is of potential relevance in patients with decompensated cor pulmonale, in whom impairment in right ventricular contractility could lead to further deterioration in clinical status.

Studies have found that nifedipine significantly reduces PAP; in addition, it decreases PVR to a greater degree than SVR in patients with abnormal pulmonary vascular resistance, suggesting that nifedipine selectively reduces PVR.[14, 31, 32, 59, 82] Nifedipine has been shown experimentally and clinically to reduce hypoxic vasoconstriction and, thus, worsen gas exchange.[93] The drug also inhibits the ability of oxygen to reduce pulmonary pressure in patients with COPD, and its use as long-term treatment for COPD-related pulmonary hypertension has therefore been questioned.

It is unclear whether the results with nifedipine can be extrapolated to other calcium blockers. Data suggest that nifedipine has the most specific pulmonary vasodilating effects.[113] Clinically, in the small series available verapamil did not have beneficial effects in the majority of patients treated. One study reported no changes in resting and exercise pulmonary hemodynamics and PaO_2 in patients with hypoxic pulmonary hypertension treated with verapamil, whereas other studies have reported a decrease in PAP with verapamil therapy.[13, 104] Untoward effects attributable to the negative inotropism of verapamil resulting in cardiac collapse have been reported.[70] Clinical experience with diltiazem is limited,[20] and conclusions regarding its efficacy in pulmonary hypertension can not yet be drawn. Diltiazem causes moderate peripheral vasodilation with mild negative inotropic and chronotropic properties and has been shown to have no adverse effects on PAP and SaO_2 in some patients with hypoxic pulmonary hypertension.[20]

Angiotensin-Converting Enzyme Inhibitors

Animal and human studies suggest that angiotensin II has an important role in mediating hypoxia-induced pulmonary vasoconstriction and pulmonary hypertension. Conversely, angiotensin-converting enzyme inhibitors prevent the development of these hypoxia-induced pulmonary vascular changes.[83] However, they have a greater effect on systemic than on pulmonary vascular tone. With the administration of angiotensin-converting enzyme inhibitors, the ratio of PVR to systemic vascular resistance tends to increase significantly. No changes in PaO_2 or venous oxygen saturation were observed in patients with primary pulmonary hypertension or in patients with congestive cardiomyopathies during treatment with angiotensin-converting enzyme inhibitors.[83]

Beta-Adrenergic Agonists

Isoproterenol elicits bronchodilatation as well as vasodilation via action on β-adrenergic receptors. In normal subjects, isoproterenol leaves PAP relatively stable whereas PVR falls. After cardiac surgery, isoproterenol was associated with a fall in arterial oxygen saturation induced by dilation of hypoxia-constricted pulmonary vessels distributing blood to underventilated lung areas.[30] β-Adrenergic agonists have an unpredictable effect on oxygenation in patients with chronic obstructive pulmonary disease.[71] In some patients, an improvement in oxygenation has been observed; this has been attributed to redistribution of ventilation facilitated by the bronchodilator effect of the drug. Isoproterenol administration in 15 patients with adult respiratory distress syndrome early in the disease produced a marked increase in cardiac output and venous admixture, with a small increase in PAP and no change in pulmonary capillary wedge pressure.[114]

Prostaglandins

Prostaglandin E_1 and prostacyclin (PGI_2) are the most promising drugs for the treatment of many forms of pulmonary hypertension. Their clinical use can be expected to increase as their pulmonary vasodilating effects become better known. PGE_1 and PGI_2 are both naturally occurring prostaglandins with almost similar structures and short half-lifes. A continuous intravenous infusion is required for safe administration. PGE_1 has the shortest half-life (1–2 minutes). The short half-life of both agents makes their use relatively safe even in critically ill patients, because adverse effects disappear shortly after discontinuation. In addition to their vasodilating actions, both agents are inhibitors of platelet aggregation[24] and have anti-inflammatory effects.[27, 99] PGE_1 and PGI_2 also appear to have mild inotropic effects.[100]

Doses of PGE_1 several times higher than those required for PGI_2 are necessary to achieve similar pharmacologic effects. One possible advantage of PGE_1 as a pulmonary vasodilator over PGI_2 is that PGE_1 is removed and metabolized by the lung endothelial cells, whereas PGI_2 is not. However, although it is commonly reported that as much as 80% of PGE_1 is removed with one passage through the lung, one study has shown that 34% of radiolabeled PGE_1 remained in the bloodstream 20 minutes after injection.[36] Systemic vasodilation usually occurs with administration of both PGE_1 and PGI_2 in doses high enough to cause pulmonary vasodilation and can cause severe systemic hypotension.[106] However, in comparison with nitroglycerin, sodium nitroprusside, and hydralazine, PGE_2 demonstrates the greatest specificity on the pulmonary circulation.[81] Adverse effects include flushing, diarrhea, and headache.

PGI_2 has been consistently shown to reduce PVR even in patients without pulmonary hypertension,[19, 102] whereas PGE_1 has been found to reduce PVR in normal individuals in some studies,[6, 26] whereas other studies have found no effect[67] or even an increase in PVR.[9] In addition, PGE_1 fails to block hypoxic pulmonary vasoconstriction in normal volunteers,[67] although it does so in animals.[54, 76] On the other hand, both PGE_1 and PGI_2 appear to be effective pulmonary vasodilators in most clinical situations complicated with pulmonary hypertension.

PGE_1 and PGI_2 Therapy in ARDS. Because increased pulmonary vascular resistance is the major pathophysiologic abnormality in ARDS, it has been postulated that pulmonary vasodilator therapy may be a useful therapeutic adjunct for ARDS. However, increased PVR can be due not only to vasoconstriction but also to intravascular obstruction (thrombi, emboli) and to extravascular compression (edema, fibrosis). In addition, although increased PVR correlates with the severity and mortality of ARDS, the increased PVR may be a result of ARDS and not itself a major contributor to outcome.

Shoemaker and Appel[1, 91] studied the hemodynamic and oxygen transport effects of PGE_1 infusion in patients with ARDS who had undergone operation. After PGE_1 infusion, they found a prompt reduction in mean PAP and PVR. Subsequently, systemic vascular resistance also decreased, and there were increases in cardiac index, oxygen delivery, and oxygen consumption. Despite the prompt reduction in pulmonary vasoconstriction, the improvement in PaO_2 was delayed, and there was no significant immediate improvement in alveolar-arterial oxygen gradient and pulmonary shunt. This is consistent with the concept that reduction of vasoconstriction in hypoxic areas of the lung may improve blood flow to the poorly ventilated lung segments, which tends to lower PaO_2 initially. However, in these studies a late improvement of PaO_2 and pulmonary shunting occurred, suggesting that these lung elements also developed improved ventilation.[1, 91]

Holcroft et al[45] evaluated a 7-day infusion of PGE_1 in surgical patients with ARDS. The drug seemed to improve pulmonary function; there was a significant decrease in the number of patients who died with severe pulmonary failure in the PGE_1-group in comparison with the placebo group. Survival at 30 days after the end of the infusion was significantly better in the patients given PGE_1, with 71% alive at this time compared with 38% of the placebo patients. The PGE_1 infusion was safe to use. It did not potentiate systemic infections and did not impede systemic wound healing. When titrated slowly and used at intravenous doses of 30 $ng/kg^{-1}/min^{-1}$, it did not cause serious decreases in systemic arterial blood pressure. Animal experiments also suggest that prostacyclin might be beneficial in acute lung injury.[98, 105] One case report described beneficial effects of prostacyclin in ARDS.[84]

These reports[1, 45, 91, 103] suggest beneficial effects of PGE_1 on PVR, cardiac output, and oxygen transport in patients with ARDS. Large-scale clinical studies are currently being conducted to confirm these observations. PGE_1 is available for clinical use, whereas prostacyclin remains an investigational drug. PGE_1 may become the "nitroprusside" of the lesser circuit for intensive care use, at least until PGI_2 becomes available.

Intravenous Fat Emulsions

Infusion of intravenous fat emulsions (IVFE) has a mixed action on the pulmonary vascular bed. When given as a bolus or rapid infusion, a vasoconstrictive response is reported; when IVFE are given as a slow infusion, a vasodilating effect is seen.[65, 94] The same mixed response is observed when arachidonic acid is infused.[46, 52] The reasons for these mixed actions are unclear, but it has been suggested that an alteration in eicosanoid production is a factor because the vasomotor response is blocked by indomethacin.[37, 48, 65] The polyunsaturated fatty acids in the IVFE serve as precursors to the eicosanoids and may thus have effects on the pulmonary vascular tone due to the production of vasoactive eicosanoids. During a slow infusion, it is likely that a net increase in vasodilating eicosanoids (e.g., PGE_1, PGE_2, PGI_2) occurs. During a bolus or rapid infusion, however, the excessive amount of substrate may overwhelm the enzymatic pathways for vasodilating eicosanoids, resulting in an increased production of potent vasoconstrictive eicosanoids, such as the thromboxanes and leukotrienes.[37] In general, the vasodilating eicosanoids have anti-inflammatory effects[37, 38, 96] in contrast to the pro-inflammatory effects of vasoconstrictive thromboxanes and leukotrienes.[38, 58, 107] It has therefore been suggested that IVFE exert a vasodilating and anti-inflammatory response when given as a slow infusion.[2, 95, 96]

Intravenous fat emulsions may have beneficial effects similar to those reported for PGE_1 and PGI_2 in ARDS, depending on the dose, duration of infusion, and fatty acid content in the IVFE.[48] If this is true, IVFE might be more effective with fewer side effects; because eicosanoids are local hormones, they could be expected to function more effectively when local synthesis is stimulated than when administered as a systemic infusion. Systemic infusion of prostaglandins results in low tissue levels with high blood levels. Infusion of IVFE can result in high tissue levels of prostaglandins with low systemic levels, thus avoiding systemic side effects.

Anesthetic Agents

A decrease in arterial PaO_2 and an increase in pulmonary shunting have been reported during anesthesia. Numerous models have been designed to study the effects of anesthetic agents on the pulmonary circulation and on hypoxic vasoconstriction. Earlier explanations centered for the most part on the effect on lung mechanics. Although changes in distribution can account for some of the findings, attenuation of the hypoxic pulmonary vasoconstriction response may have an influence on the gas exchange during anesthesia. In general, hypoxic pulmonary vasoconstriction is not directly inhibited by intravenous anesthetic agents but is directly inhibited by inhalation agents.[25] Clinically, the effect of anesthetics on PVR must be taken into account as one possible factor when the causes of hypoxemia under anesthesia are considered.[25] The selection of anesthetic agent can be of importance in minimizing arterial hypoxemia in patients with severe gas exchange problems. However, the inhibition of hypoxic pulmonary vasoconstriction is usually of little clinical importance. Currently, inhalation agents are not believed to be contraindicated for thoracic surgery with one-lung ventilation when the hypoxic pulmonary vasoconstriction response is desirable.[6] In patients with lung abnormalities in whom hypoxemia may occur, a change to an intravenous agent should be considered.[72]

SUMMARY

The pulmonary circulation is a low-resistance, highly compliant vascular bed that is markedly influenced by pressures generated by the heart and the thorax. Normally, it appears to be maximally dilated, uninfluenced by maneuvers to decrease its initial tone. Because of its intrinsic properties and its meager endowment for vasomotor control, modest external forces can exert relatively large hemodynamic effects, complicating attempts to distinguish between active and passive changes in vascular calibers.

The ideal pulmonary vasodilator for the treatment of pulmonary hypertension in the intensive care unit would preferentially produce pulmonary versus systemic vasodilation and would have minimal effect on intrapulmonary shunt. Increasing the ratio of tissue oxygen delivery to oxygen consumption can improve the survival of critically ill patients, including those with respiratory failure. However, in situations of ventilation/perfusion mismatch, the use of vasodilator drugs to augment cardiac output could worsen venous admixture. Of the currently available agents, nitroglycerin and PGE_1 infusion appear to have the best ratio of pulmonary to systemic vasodilation. The pulmonary vasodilating drugs can have significant adverse effects, and clinical trials are needed to document their overall safety and efficacy. Careful monitoring of pulmonary and systemic hemodynamics and arterial oxygenation is needed when pulmonary vascular tone is directly manipulated by vasoactive drugs or anesthetics.

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Extracorporeal Methods in the Intensive Care Unit

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In the intensive care unit, a host of life-threatening problems may necessitate the use of extracorporeal methodology. Critically ill patients with poisonings, renal failure, fluid overload, or hyperviscosity syndrome may need substantial modification of the composition, volume, or both of the body fluids. The particular extracorporeal method employed is determined largely by the condition to be treated, the clinical status of the patient, and the specific goals of therapy.

In this review, several extracorporeal methods—hemodialysis, hemofiltration, continuous arteriovenous hemofiltration, and plasmapheresis—are reviewed. Extracorporeal methods used to support ventilation in patients with the adult respiratory distress syndrome are briefly reviewed. Peritoneal dialysis, although not strictly an extracorporeal technique, is also discussed. Peritoneal dialysis is similar in both purpose and principle to the other methods and is employed frequently for the same problems in the intensive care unit. The basic principles underlying all of the techniques, the specific methodologies, indications, and contraindications for each, and the expected results of the treatments are presented. We hope the resulting overview will assist the intensivist in the management of critically ill patients.

INTRODUCTORY CONCEPTS

All extracorporeal methods are designed to achieve common objectives, that is, to alter the composition or volume or both of the various body fluids. These objectives are accomplished by utilizing the principles of diffusion, convection, adsorption, and centrifugation, alone or in combination. Because the processes of diffusion and convection have major roles in most of the extracorporeal methods, they are described in greatest detail.

Diffusion is the continual movement of molecules among each other in liquid or gases. When a membrane separates two solutions, molecules diffuse across the membrane according to the electrochemical (charge and concentration) gradients

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for each molecular species. The permeability of the membrane to each molecule and the total area available also importantly influence the rate and, thus, the amount of diffusion. In the techniques and clinical conditions discussed in this review, concentration gradients and specific membrane permeability characteristics have the most important roles in governing diffusion. The extracorporeal methods that rely on diffusion (hemodialysis, peritoneal dialysis) utilize a semipermeable membrane that separates the blood from some other fluid (dialysate). Dialysate solute concentrations are selected to achieve a concentration gradient for the desired solutes from the blood to the dialysate fluid. Solute size, charge, protein binding, and blood viscosity can alter the diffusability of solutes. Membrane permeability can be selected in hemodialysis by choosing a specific membrane material with specific surface area. In peritoneal dialysis, the membrane (peritoneum) and its surface area (related to body surface area and splanchnic blood flow) are less well characterized and cannot be selected.

In practice, the concentration gradient, determined by the blood and dialysate solute concentration on opposite sides of the particular membrane, determines the net movement of solute into or out of the blood. As movement proceeds and concentrations move toward equilibrium, decreased movement of that solute occurs across the membrane.

Convection is the movement of dissolved or suspended molecules in fluids (or gases) in association with hydrostatic or osmotic pressure-mediated flow. The rate of fluid (solvent) movement across a semipermeable membrane is determined by the transmembrane pressure gradients, the membrane surface area, and the hydraulic conductivity (permeability) of the membrane. The transfer of solutes in fluid across a membrane is clearly facilitated by bulk flow of liquid in the same direction (solvent drag) and inhibited by the bulk flow of liquid in the opposite direction. In practice, extracorporeal techniques that utilize convection (hemofiltration, hemodialysis, peritoneal dialysis) regulate the hydrostatic or osmotic pressure or both of the blood, dialysate fluid, or both to promote the desired bulk flow of solvent (fluid). When possible, specific membranes with desirable hydraulic permeabilities are selected to enhance the convective transfer of fluid.

SPECIFIC EXTRACORPOREAL TECHNIQUES

Hemodialysis

Technical Considerations. Hemodialysis utilizes both diffusion and convection to alter blood composition. In practice, hemodialysis is performed by withdrawing blood continuously from the circulation, pumping it through plastic tubes (or over plates) that serve as a semipermeable membrane. A dialysate solution (containing salts and other solutes) bathes the other side of the membrane. Continuously pumping the blood and dialysate at specific flow rates permits maintenance of concentration gradients for appropriate diffusion. Adjustment of resistance to flow permits the creation of hydrostatic and pressure gradients. When coupled with the ability to alter oncotic forces in the blood and dialysate, convection of fluid in the desired direction also can be accomplished. Large amounts of solute can be cleared and large volumes of fluid ultrafiltered by hemodialysis. Typical blood flow rates during hemodialysis are between 200 and 300 mL per minute, and dialysate flows of 500 mL per minute are easily accomplished.

Clearance of a solute reaches a maximum at specific blood and dialysate flows; there is a point beyond which increases in blood flow are not accompanied by increases in solute clearance. This plateau in the blood flow/solute clearance ratio occurs because concentration gradients have been maximized and membrane area and permeability characteristics now limit diffusion. Moreover, because effective membrane permeability decreases as solute size increases, the maximum clearance of large molecules occurs at lower blood flow rates than that for smaller molecules. For example, the clearance of urea (a small molecule) reaches maximum at a much higher flow rate than that achieved during clearance of creatinine (a larger solute).

Ultrafiltration, the transmembrane movement of a fluid (ultrafiltrate) in response to hydrostatic and oncotic pressures, can be moderated by positive pressure on the blood side of the dialysis membrane and (using the appropriate dialyzer) negative pressure on the dialysate side of the membrane. The ultrafiltrate has a chemical composition similar to that of plasma except for the absence of proteins, which are excluded from transfer by the membrane. Convective transport with solvent drag accounts for some solute transport during ultrafiltration, and this adds to the total solute removal by hemodialysis.

Clinically, ultrafiltration during hemodialysis is used for the removal of excessive fluid in the treatment of fluid overload in uremia. When fluid removal is not desired, the ultrafiltrate can be minimized or replaced by an electrolyte solution, thereby further modifying the chemical composition of the plasma. Isolated ultrafiltration ("dry dialysis") utilizing convective forces without diffusion to form ultrafiltrate can be accomplished by not using a dialysis bath. Pulmonary edema secondary to ischemic and valvular heart disease[155] as well as chronic edematous states secondary to kidney disease have been treated with isolated ultrafiltration.[148] Isolated ultrafiltration is generally more hemodynamically tolerated than regular hemodialysis.[57, 127] At ultrafiltration rates of 400 to 500 mL per hour in regular hemodialysis, complications such as cramps, headaches, and hypotension are more common than in isolated ultrafiltration. The complications are most likely secondary to rapid changes in blood chemical composition rather than to intravascular volume depletion only. Decreasing the dialysis rate or administration of intravenous mannitol or both helps reverse these complications. Mannitol therapy may also help by mobilization of edema fluid to reexpand the intravascular volume during dialysis.[148]

Indications for Hemodialysis. Renal failure with incipient or overt uremia is the most common indication for hemodialysis. Other indications are electrolyte disorders (hyperkalemia, hypercalcemia, acidosis), fluid overload, and the need to remove dialyzable toxins.[40] The development of acute renal failure in the hospitalized sick patient is associated with a substantially increased mortality rate that can be decreased with aggressive supportive treatment. Hou et al found that in 4.9% of patients admitted to Tufts New England Medical Center, renal insufficiency developed.[66] Of 129 patients, 10 (7.8%) had severe renal failure necessitating dialysis. Jochimsen et al[75] prospectively evaluated 4130 admissions to the intensive care unit at The Free University of Berlin. Renal insufficiency developed in 274 patients. Seventy-three patients received dialysis. Of the 201 patients with renal failure who did not receive dialysis, 40 might have required this treatment but did not because of "do not resuscitate" orders. Thus, renal failure is common, and the need to provide hemodialysis in the intensive care unit may extend to a large percentage of patients admitted.

In the absence of emergent indications for dialysis, several studies have suggested the desirability of initiating early dialysis in acute renal failure in the intensive care unit patient. Dialysis begun before blood urea nitrogen exceeds 100 to 120 mg/dL is associated with a decreased mortality rate, especially in patients with multiple surgical, medical, and infectious problems that render them catabolic, increase their nutritional needs, and obligate the administration of large volumes of fluid and solutes.[26, 86, 157] Thus, "prophylactic" dialysis should be considered in appropriate clinical circumstances.

Advantages of Hemodialysis. The principal advantage of hemodialysis is the high clearance rate that can be achieved quickly. This is especially helpful in the clinical setting in which rapid solute removal (i.e., hyperkalemia) is needed. Urea clearance rates of 150 mL per minute can be accomplished during hemodialysis (equivalent to a urea clearance rate of 135 L per week if the patient receives 15 hours of hemodialysis). The high clearance rates also permit the treatment time to be reasonably limited, thus, allowing the intensivist to provide other essential critical care to the patient without interference.

Disadvantages and Complications of Hemodialysis. The disadvantages of hemodialysis include the need for special equipment, the need for trained medical and nursing personnel, and the need for adequate vascular access. There are also major potential complications, including hemodynamic instability, pulmonary dysfunction, complications related to vascular access, and difficulties with the anticoagulation that is often required.[74] Some of these problems will be addressed in detail.

In an intensive care unit setting, emergent vascular access to patients is frequently needed for the initiation of hemodialysis. The first technique to accomplish this, the placement of an external arterial venous shunt in an extremity, was described by Quinton and colleagues[135] in 1966. For the most part, this approach has now been abandoned, having been replaced by the techniques of percutaneous venous catheter insertion into the subclavian vein (semipermanent) or, occasionally, the femoral vein (temporary).

Retrospective analysis suggests that subclavian vein cannulation for hemodialysis is associated with less infection, thrombosis, and hemorrhage than that with external shunts.[34] Once placed, the subclavian catheter can be used for many dialyses, obviating the need for repeated painful femoral vein cannulation. Moreover, percutaneous subclavian vein cannulation preserves peripheral veins that may be needed for other critical care treatments or even for subsequent arteriovenous fistula formation should chronic hemodialysis be necessary.

The type of access selected for use in the patient in the intensive care unit setting is best determined by the estimated period for which dialysis will be required. Patients who may require only several dialysis treatments can be managed with intermittent cannulation of the femoral veins. Patients who will most likely need dialysis for longer periods of time should have percutaneous venous catheter placement into the subclavian or internal jugular veins. Presently available catheters have a double lumen and are designed for bidirectional flow, thus, eliminating the need to cannulate a second vessel.[119]

Immediate complications of central venous catheter placement include inadvertent arterial puncture, pneumothorax,[107] hemothorax, air embolism,[107] hematoma, deep vein thrombosis,[85] vena cava perforation, and cardiac perforation with tamponade.[18, 59] Late complications include infection, thrombosis, and stenosis of subclavian or central veins.[116] Even in patients without clinical evidence of thrombus formation and with satisfactory blood flow, venography can reveal unsuspected thrombosis, stenosis, or both. Edema of the ipsilateral arm secondary to subclavian vein stenosis can develop within a few weeks or as much as 25 months after the placement of an arteriovenous fistula.[153]

Inadequate blood flow is seen in as many as 6.2% of catheters placed for acute hemodialysis. Inadequate flow may be secondary to catheter kinking, malpositioning of the catheter, or thrombus formation at the orifice.[163]

All extracorporeal methods expose blood to artificial membranes. In hemodialysis this can lead to activation of the clotting cascade, which results in coagulation within the dialyzer and the loss of substantial quantities of blood. Thus, anticoagulation during hemodialysis (and other extracorporeal methods) is usually necessary. Unfortunately, many patients in the Intensive Care Unit have relative or absolute contraindications to systemic anticoagulation, such as recent surgery, active bleeding, or a central nervous system hemorrhage. This has led to the development of alternative methods to prevent clotting of extracorporeal blood circuits. One such method is regional heparinization, which involves the infusion of heparin into the blood line from the patient to the dialyzer (the "arterial" line) with simultaneous infusion of an equivalent dose of protamine into the line returning blood to the patient (the "venous" line).[103] While seemingly effective, regional heparinization is difficult to regulate properly, and patients are often over- or underanticoagulated.[56, 156] More precise methods of heparin administration,[37, 84] low molecular weight heparin,[62, 95] prostacyclin,[171] and citrate[38, 144, 168] also have been used as alternatives to standard anticoagulation with heparin, with some success. The ideal solution, hemodialysis without anticoagulation, has been achieved through the use of hollow fiber membranes coupled with intermittent or constant saline infusions.[22, 23]

Hypoxemia is a well-described phenomenon during hemodialysis.[20, 30] At least two probable mechanisms are responsible for this abnormality.[36, 54] The first mechanism involves hypoxemia associated with leukopenia and evidence of complement activation and is characterized by a decrease in pulmonary oxygen diffusing capacity and an increased alveolar-arterial oxygen gradient.[27, 99] This hypoxemia is dependent on the specific dialysis membrane and occurs to a greater extent with cellulosic membranes than with polyacrylonitrile and polymethylacrylate fiber membranes.[29] The cellulosic membrane has a greater propensity to activate complement, causing leukoagglutination and pulmonary leukocyte sequestration, which results in a usually temporary hypoxemia during the hemodialysis procedure.[55] The second mechanism of dialysis-associated hypoxemia is characterized by hypoventilation and a normal alveolar-arterial oxygen gradient. Carbon dioxide is removed from the extracorporeal dialyzer, and blood with a low $PaCO_2$ is returned to the patient.[145] This results in hypoventilation by the patient secondary to a low $PaCO_2$, leading to a low PaO_2, decreased respiratory quotient, and evidence of decreased neuromuscular ventilatory drive.[29, 130] This form of dialysis-associated hypoxemia is independent of dialyzer membrane type and occurs when acetate, but not bicarbonate dialysate solution, is employed.[29, 33]

Multiple studies have been performed on the hemodynamic effects of hemodialysis. Most studies have included patients receiving chronic hemodialysis, and it is clear that the results of these studies cannot be applied to patients receiving acute hemodialysis in the intensive care unit. Hypotension is the most frequently observed adverse hemodynamic effect of hemodialysis. The etiology of hypotension is often multifactorial and is beyond the scope of this review, although it has been reviewed extensively elsewhere.[24, 63, 82, 83, 132] What seems clear is that hypotension may be precipitated not only by changes in blood volume but also by a failure of normal compensatory volume regulation mechanisms in the presence of mild volume loss. The defects include inadequate pulse increases, inappropriate vasodilation, and failure to augment cardiac output during stress.[7, 167] As noted previously, isolated hemofiltration is more tolerated than routine hemodialysis, perhaps by preservation of plasma composition or osmolality.[65, 138] In practice, dialysate solutions also can be used that maintain plasma osmolality to help stabilize blood pressure during hemodialysis.

Not all hemodynamic effects of dialysis are adverse. Uremic cardiomyopathy may improve after adequate hemodialysis as a consequence of increased cardiac contractility independent of alterations in cardiac output of blood volumes.[120] The positive inotropic effect may be related to increased ionized calcium[64] or to the removal of uremic toxins that may impair left ventricular contractility.[6, 69]

Continuous Arteriovenous Hemofiltration

Technical Considerations. Continuous arteriovenous hemofiltration is an extracorporeal method in which fluids, electrolytes, and nonprotein-bound molecules are removed from the blood solely by ultrafiltration of plasma.[9, 117] Arterial blood driven by arterial pressure is directed through a filter with high hydraulic conductivity to water and small solutes but selective impermeability to proteins and cells. The arterial blood pressure not only moves blood through the extracorporeal circuit but also provides the hydrostatic pressure gradient necessary for ultrafiltration. Net ultrafiltration pressure also may be increased by applying a negative pressure (vacuum) on the outside of the filter.[70] The blood, free of ultrafiltrate, with an increased concentration of proteins and cells is returned to the body through a venous line. Typically, arteriovenous hemofiltration does not obligate the use of a blood pump. Depending on the particular patient needs, the specific amount of volume to be removed, and the desired modification in plasma composition to be achieved, a crystalloid or colloid solution can be added to the venous return and administered to the patient. Because the removed fluid has a composition similar to that of serum, the arteriovenous hemofiltration technique can also remove waste substances, toxins, or both, but only in amounts contained in the discarded ultrafiltrate.[53, 125] The removal is substantially less than that achieved by regular hemodialysis, making this technique less effective for the treatment of uremia per se.

Ultrafiltration rates are directly related to the hydrostatic pressure gradient across the ultrafilter (arterial pressure plus any applied negative pressure), the oncotic pressure of the blood, the blood viscosity (which modifies blood flow), the venous resistance to blood return (which modifies flow and pressure), and, of course, the specific characteristics of the filter for solute and water transfer. Adequate ultrafiltrate formation can occur with a systolic pressure as low as 50 to 70 mm Hg,[93] especially if negative pressure is applied to the outside of the filter.[70] Of course, higher blood pressures are associated with increased ultrafiltration rates and are desired to facilitate the procedure. Blood flow rates also significantly affect ultrafiltration, with rates of greater than 100 mL per minute leading to increased intrafilter pressure and increased ultrafiltration. The location of the arterial cannula is also important. In patients with low blood pressure, it may be necessary to cannulate a large femoral artery to secure adequate flow. In selected instances, a blood pump may be needed to maintain adequate ultrafiltration rates, but this makes the procedure more technically complicated.[93] With well-placed cannulas and negative external pressure (and the use of a pump when needed), ultrafiltration rates of 6 to 16 mL per minute (360–960 mL/hour) can be achieved, even in critically ill patients. Removal of this volume of fluid can be helpful in patients with anasarca, can remove a significant amount of waste solute, and can even permit aggressive administration of adequate volumes for parenteral hyperalimentation, even in patients with renal failure.[79, 91] The application of a 200-mm Hg vacuum to the ultrafiltration compartment can double the rate of fluid removal, increasing its efficiency.[77, 80] With the technique of "predilution," increased rates of urea clearance can be achieved.[78] Predilution is the administration of crystalloid into the arterial line, which dilutes the red cells and proteins, lowers viscosity (by decreasing hematocrit and plasma protein concentration), and increases the removal of solutes by convection. Some percentage of the predilution fluid will be ultrafiltered, thus, reducing the net volume removed from the patient. Moreover, predilution interferes with the measurement of ultrafiltrate chemistries and prevents their use in estimating solute removal from the patient.

Advantages of Continuous Arteriovenous Hemofiltration. Continuous arteriovenous hemofiltration can be initiated rapidly in critically ill patients. It can be employed at the bedside and may interfere less with other critical care treatments. Moreover, the procedure can be managed by the intensive care unit staff without the need for other special equipment or specially trained personnel.[128] It is well-tolerated hemodynamically by most patients, even those with low blood pressures.

Ultrafiltration rates and ultrafiltrate chemistries can be measured easily, permitting the control of body volumes and the regulation of blood solute concentrations. As noted previously, large quantities of fluid can be removed from edematous patients or from patients with inadequate urine output who require hyperalimentation or other large volume fluid administration.[68, 106] Although absolute solute clearance rates are less than those for hemodialysis, continuous arteriovenous hemofiltration, which is often used for prolonged periods of time, may sometimes be adequate to control uremia or other chemical or toxic crises in critically ill patients.[105, 125]

Disadvantages and Complications of Continuous Arteriovenous Hemofiltration. The major disadvantage of continuous arteriovenous hemofiltration relates to the need to establish both arterial and venous vascular accesses. Other problems relate to the possible clotting of the filter, which obligates anticoagulation, and to the potential for hemodynamic instability resulting from excessive fluid removal with inadequate replacement. Hemorrhage is a well-described complication of continuous arteriovenous hemofiltration, and various types of anticoagulation techniques have been employed to reduce the risk of hemorrhage.[133] As in regular hemodialysis, none of the methods are completely successful.

Because continuous arteriovenous hemofiltration depends on ultrafiltration without diffusion, it is impossible to achieve substantial solute clearance unless large volumes of ultrafiltrate are removed and replaced with crystalloid or colloid solution. In one study, the occurrence of hypotension and tachyarrhythmias was actually more common during continuous arteriovenous hemofiltration than during hemodialysis when corrected for similar rates of urea clearance.[87] Thus, the technique is not ideal for the treatment of patients with renal failure who are not complicated by massive fluid overload. It should be reserved for the appropriate circumstances in which it is most effective.

Continuous Arteriovenous Hemodifiltration

Continuous arteriovenous hemodifiltration combines the techniques of dialysis with hemofiltration.[13, 44, 112] In addition to diffusion dialysis, which enables increased clearance of solutes, convective ultrafiltration enables increased fluid removal. The dual goals are accomplished by circulating dialysate in the ultrafiltrate chamber outside the specialized ultrafiltration membrane. Various types of filters have been used. Dialysate may be circulated by gravity or by a pump in circuit, while the blood is circulated by arterial pressure or by a pump (as described previously). Increasing dialysate flow rates leads to increased urea and other solute clearances. The ultrafiltration rate responds as expected to changes in transmembrane hydrostatic and oncotic pressure gradients as described previously.[139]

Continuous arteriovenous hemodifiltration can provide urea clearance rates of 10 to 37 mL per minute (urea clearances of 19–23 L per day). This rate compares favorably to the 30 to 40 L of urea clearance achieved during 4 hours of hemodialysis.[100, 131] Arteriovenous hemodifiltration can be alternated with continuous arteriovenous hemofiltration to manage renal failure and fluid overload, such as that occurring in patients with hypercatabolic renal failure who require the administration of large volumes of parenteral hyperalimentation as well as dialysis.[100, 139] It may succeed where separate techniques would fail.

Advantages of Continuous Arteriovenous Hemodifiltration. The principal advantage of continuous arteriovenous hemodifiltration is the added solute clearance. The technique seems to maintain the hemodynamic stability of hemofiltration alone. Although there are no controlled studies comparing continuous arteriovenous hemodifiltration to hemodialysis, several reports have demonstrated that hemodifiltration is well tolerated in critically ill patients.[12, 46, 165] Stevens et al[154] used continuous arteriovenous hemodifiltration in 36 patients who were considered too unstable for hemodialysis. The treatment did not result in cardiovascular instability or increased oxygen requirement in any of the patients, the majority of whom were mechanically ventilated and were receiving inotropic agents for hemodynamic support.

Disadvantages and Complications of Continuous Arteriovenous Hemodifiltration. Continuous arteriovenous hemodifiltration shares similar problems with hemofiltration; principally, the need for arterial and venous access and the need for anticoagulation. The incidence of bleeding varies in different studies. No overt bleeding was noted during continuous arteriovenous hemodifiltration in the patients described by Stevens et al,[154] but other studies have not reported this low complication rate.[46] Hyponatremia secondary to the use of dilute dialysate solution and the accidental infusion of dialysate into the patient also have been reported.

Peritoneal Dialysis

Technical Considerations. Peritoneal dialysis does not employ an extracorporeal blood circulation and, by strict definition, is not a true extracorporeal treatment. However, the technique of peritoneal dialysis is dependent on the same physical principles in hemodialysis. In addition, it is frequently employed for the same indications that hemodialysis is employed for, in the same types of patients in the intensive care unit. The mechanism of peritoneal dialysis is based on the fact that the peritoneum is a semipermeable membrane with a substantial splanchnic blood supply. When dialysate is placed in the free peritoneal cavity, fluids and solutes exchange between the blood and dialysate by the identical processes of diffusion and ultrafiltration that pertain to hemodialysis.[32, 102, 113] Ultrafiltration occurs in response to osmotic gradients between the peritoneal dialysate solution and blood.[160] The dialysate solution osmolality (and, thus, ultrafiltration) can be varied by adjusting its glucose concentration. At any osmotic strength, ultrafiltration rates are maximal immediately after the introduction of dialysate into the peritoneum. The osmotic gradient (and the ultrafiltration rate) decreases as glucose is absorbed into the blood and as solutes diffuse from the blood into the dialysate. As both processes dissipate, the osmotic gradient and ultrafiltration rate decrease, and the rate approaches the rate of lymphatic absorption through stomata, mostly located in the diaphragm.[98] In studies of patients receiving chronic ambulatory peritoneal dialysis, lymphatic absorption rates of 89.5 ± 11.8 mL per hour have been observed. If these rates were applied to critically ill patients receiving peritoneal dialysis in the Intensive Care Unit, that amount of lymphatic absorption could reduce net ultrafiltration by more than 80% and daily urea clearance by more than 16%.[97]

Solute transfer in peritoneal dialysis occurs both by diffusion and by convection (solute drag during ultrafiltration). Diffusion is influenced by the concentration gradient across the peritoneum, the effective peritoneal membrane area, and the actual permeability characteristics of the peritoneal membrane. Diffusion proceeds through intracellular junctions in the peritoneal membrane and, thus, may be modified by diseases of the peritoneum.[122, 123] The overall efficiency of peritoneal dialysis depends on many factors, including the volume and composition of the dialysate solution, the dialysate flow rate, the effective splanchnic blood flow, the state of the peritoneal membrane, and the relative contribution of abdominal lymphatic absorption.[101, 102, 123, 124] The actual efficiency of peritoneal dialysis is therefore unpredictable and must be determined by empirical observation during the procedure. In many patients, the technique is adequate, but in some it is not.

Acute peritoneal dialysis necessitates the placement of an intraperitoneal catheter to infuse and then remove dialysate. Placement can be accomplished by a percutaneous technique at the bedside for temporary dialysis (one to two treatments) or by surgical placement of a more permanent soft catheter (Tenckhoff catheter) for longer term peritoneal dialysis. Placement of the catheter in the peritoneum may be limited by peritoneal fibrosis or adhesions, which can contraindicate the procedure. The presence of a fresh abdominal wound or surgical drain can create fluid leaks and complicate measurements of dialysate outflow or lead to peritoneal infection. Nonetheless, in most patients, catheter placement can be accomplished, and the procedure can be performed in most intensive care units with specially trained personnel.

Comparison with Hemodialysis. Hemodialysis and peritoneal dialysis utilize the same forces of ultrafiltration and diffusion. Peritoneal dialysis is associated with a lower clearance of small molecules, such as urea, but because it is carried out for longer periods of time, can result in satisfactory solute clearance. The clearance of larger molecules (the so-called middle molecules) may actually be more efficient in peritoneal dialysis than in hemodialysis and has been advanced as a relative benefit of the procedure.[123] Maximal urea clearance rates for peritoneal dialysis are 30 to 40 mL per minute which provides as adequate a treatment of renal failure as hemodialysis.

Advantages of Peritoneal Dialysis. Peritoneal dialysis can be initiated rapidly after placement of the peritoneal catheter.[76] It can be performed by the intensive care unit staff and does not require complicated special equipment or specially trained personnel. There is no need for systemic anticoagulation or access to the vascular system, as in hemodialysis. Moreover, the dialysis is slow (gentle) and, therefore, well tolerated by most patients.

Disadvantages of Peritoneal Dialysis. One major disadvantage of peritoneal dialysis is the relatively low solute and fluid clearance in comparison with that of hemodialysis. Peritoneal dialysis may therefore be inadequate to control uremia in hypercatabolic patients with acute renal failure or to remove adequate volumes of fluid acutely in overloaded patients. If cardiac output and blood pressure are low, limiting splanchnic blood flow, dialysis will be very inefficient and inadequate.

Complications of Peritoneal Dialysis. Peritoneal dialysis is associated with frequent and important complications.[121, 162] In one study, major complications occurred in 3.5% of 248 patients.[140] Bowel perforation has been estimated to occur during less than 1% of peritoneal catheter placements.[142] Bowel perforation should be suspected when there is failure of return of instilled dialysate, when dialysate is feculent, or when watery diarrhea with a high concentration of glucose is noted.[141, 149] Bowel perforation can frequently be managed conservatively with intraperitoneal antibiotics and replacement of the catheter at a different site.[141, 142] However, it may mandate exploratory surgical intervention if conservative treatment fails. Peritonitis from contamination of the tubing or fluid, severe hyperglycemia from excessive glucose absorption,[41, 51] respiratory dysfunction from interference with diaphragmatic function,[3, 49, 51, 150] pleural effusions from transdiaphragmatic fluid leakage,[45, 52, 96, 143] and loss of proteins[15, 16, 81] into the dialysate from the peritoneal membrane are additional serious complications of peritoneal dialysis. Pain is the most common complication and frequently occurs early after initiation of the procedure. Pain during infusion of dialysate may be related to its acidity or to overdistention of the abdominal cavity. Adding small amounts of lidocaine to the dialysate may be helpful. Pain during drainage of the dialysate may be related to a siphoning action of the catheter, which traps the omentum or the bowel, and frequently can be ameliorated by repositioning the patient.

Plasmapheresis

Technical Considerations. Plasmapheresis is the removal of some or all of the components of plasma. Clearly, the removal of plasma is limited by the tolerance of the patient's circulation to the loss of volume. Plasma exchange permits the removal of significant amounts of plasma by replacing the removed volume with an appropriate amount of crystalloid or colloid solution or new fresh plasma to maintain circulatory homeostasis. To remove plasma, the cellular components of the blood must first be separated.[161] This can be accomplished manually by removing an amount of anticoagulated whole blood from the patient, centrifuging it, and returning the cells to the body. This was the method used by Abell et al[1] in their original description of plasmapheresis in 1914. However, manual plasmapheresis is slow and laborious. It also necessitates the handling of blood, with all of the attendant infectious risks to the patient and therapist. Manual pheresis has now been replaced by automated pheresis, accomplished either by centrifugation or by membrane filtration.[5, 60, 129]

Centrifugation plasmapheresis can be performed intermittently or continuously. During intermittent centrifugation, blood in a sterile extracorporeal circuit is pumped into a centrifugation chamber. After separation is completed and the centrifuge is stopped, the plasma is collected and the separated cellular elements are returned to the patient with replacement fluid if indicated. Continuous flow centrifugation plasmapheresis is accomplished in a chamber in which blood is exposed to centripetal force, separating plasma and cells along a density gradient. The components (plasma, platelets, leukocytes, erythrocytes) can be extracted continuously by removal from the appropriate place in the gradient. The continuous flow method increases the speed at which plasma exchange can be accomplished, permits the use of a smaller extracorporeal circuit, and permits the selective removal of cellular elements.

Membrane filtration plasmapheresis utilizes a filter of very specific pore size to separate plasma from cellular components.[19, 152] Blood is pumped through a filter that is highly permeable to water and small electrolytes and less permeable to large proteins and to cells. Membrane filtration cannot discriminate between proteins and different cellular components. To accomplish more selective separation, two filters can be used in series.[2] The first filter separates plasma from cells, and the second filter (which is more selective) separates large molecular weight plasma proteins from smaller molecules in the plasma. The proteins can be discarded if they are part of the disease process or can be returned to the patient if removal of cells is the objective of the pheresis.

An even more selective removal of plasma components can be accomplished by plasma adsorption.[8] Plasma is passed through columns containing an adsorbent material relatively specific for a particular plasma factor. The plasma is returned to the patient with all of its components except for the adsorbed material. This type of plasmapheresis can efficiently remove disease-causing blood or plasma factors, such as autoantibodies, immune complexes, and monoclonal proteins.

Indications for Plasmapheresis. Plasmapheresis has been used to treat more than 100 different disease states.[5] Unfortunately, most reports of its use are anecdotal, and a review of the literature indicates a lack of randomized, placebo-controlled prospective studies of this modality. Thus, it is difficult to list the appropriate indications or the true value of plasmapheresis.[146, 164] However, several conditions encountered in the intensive care unit seem to improve with plasmapheresis.[60, 61]

The hyperviscosity syndrome secondary to paraproteinemia seems to provide a clear indication for plasmapheresis.[5] Plasmapheresis can rapidly lower protein levels and decrease measured serum viscosity.[21, 43, 72] The lowered viscosity correlates well with improvement in the patient's clinical condition.[134] Diseases caused by circulating inhibitors of clotting factors can be treated with plasmapheresis. Slocombe et al[151] employed plasma exchange to prevent and control hemorrhage in patients with levels of Factor VIII inhibitor that were too high to be treated by infusion of Factor VIII. Plasma exchange decreased inhibitor levels sufficiently to permit the subsequent infusion of Factor VIII in amounts adequate to obtain hemostasis. Plasmapheresis with exchange of fresh frozen plasma as the replacement fluid also has been used to treat thrombotic thrombocytopenic purpura.[39, 115] Mortality rates in plasmapheresed patients decreased from 41 to 17% in comparison with those in historical controls,[94] although these patients also received other therapies in addition to plasma exchange. The HELLP Syndrome—eclampsia with hemolysis, elevated liver enzymes, and low platelet count—has also benefited from plasma exchange therapy.[104]

Immune-mediated neurologic dysfunction has been treated with plasmapheresis based on the assumption that an unknown serum factor may have a role in its pathogenesis. Anti-acetylcholine antibodies have been demonstrated in approximately 80% of patients with myasthenia gravis.[158] Complement activation and cell-mediated immune dysfunction also may be involved. Kornfeld et al[90] found that plasmapheresis was of value in 12 of 16 patients with myasthenia gravis who did not respond to steroids, thymectomy, and anticholinesterase. However, in another small study of patients with chronic myasthenia gravis, the addition of plasmapheresis to immunosuppressive therapy provided no additional benefit.[28] The role of plasmapheresis in preparation for thymectomy is unclear. Huang et al[67] retrospectively reviewed the outcome in 74 myasthenic patients without thymoma who underwent thymectomy. A total of 30 patients received preoperative steroids, 7 patients received preoperative plasmapheresis, 14 patients received both preoperative steroids and plasmapheresis, and 23 patients received no preoperative treatment. Four episodes of myasthenic crisis and five episodes of respiratory failure (requiring prolonged ventilatory support) were noted postoperatively, all in the group that received no preoperative treatment. In another study, 37 patients undergoing thymectomy were examined retrospectively by d'Empaire et al.[31] Patients who received preoperative plasma exchange had a significantly decreased time of mechanical ventilation and spent less total postoperative time in the intensive care unit. There was no mention of concomitant steroid use in these patients, making the interpretation of the efficacy of plasmapheresis difficult. In another uncontrolled retrospective study, Bolouki and Schwartzman[17] reported no episodes of respiratory failure or major pulmonary complications among 32 patients with stage II and III myasthenia gravis treated with high-dose steroids alone. Presently, plasmapheresis appears to be of some benefit in myasthenic patients with acute deterioration or with life-threatening weakness from involvement of respiratory muscles. This therapy may be particularly helpful while awaiting the effect of immunosuppressive therapy or in preparation for thymectomy. Plasmapheresis can, however, cause worsening of myasthenic symptoms.[47] This adverse effect may be related to the use of citrate as anticoagulant and the effect of citrate on serum calcium levels.[147, 169]

Antiperipheral nerve myelin antibodies have been demonstrated in the serum of patients with Gullian-Barré syndrome.[158, 159] Several studies have demonstrated the value of plasmapheresis in patients with this condition.[92, 110] The Guillain-Barré Study Group found that patients who received plasmapheresis were more likely to have clinical improvement in their clinical condition at 4 weeks, needed less time to improve one clinical grade and to walk without assistance, and were more likely to have a better outcome at 6 months. Of patients requiring mechanical ventilation, those who were randomized to receive plasmapheresis spent less time on mechanical ventilation than those patients not receiving plasmapheresis (9 versus 23 days). When mechanical ventilation was required before randomization, no difference in duration of mechanical ventilation between the two groups was found.[108] Multivariate analysis identified older age, time from onset of illness of 7 days or less, need for ventilatory support, and mean amplitude of compound muscle action potential on stimulating distally of 20% normal or less as correlating with a poor prognosis.[109] The French Cooperative Study on Plasma Exchange demonstrated similar results in patients with Guillain-Barré syndrome. They found that after randomization, 21% of patients treated with plasma exchange needed mechanical ventilation versus 46.6% of controls not receiving plasmapheresis. No benefits could be seen when fresh frozen plasma was compared with albumin as a replacement fluid. Pneumonia, systolic blood pressure instability (a fall of more than 40 mm Hg), and bradycardia (a decrease of more than 20 bpm) occurred less frequently in patients who underwent plasma exchange. However, septicemia was more common in those patients who received plasma exchange therapy. These investigators suggested that this complication may have been a consequence of the repeated vascular punctures required in the pheresis treatment group.[136] Taken in sum, these data support the role of plasmapheresis in the management of Guillain-Barré syndrome.

Complications of Plasmapheresis. The Canadian Apharesis Study Group, which reviewed 5907 exchanges in 700 patients, observed adverse effects in 12% of patients. Most reactions were minor, consisting of circumoral paresthesias, mild hypertension, mild hypotension, and hives.[137] Patten[129] has also provided an excellent review of the complications of plasmapheresis.

Extracorporeal Methods in Sepsis

Multiple mediators are believed to have a role in the pathogenesis of the cardiopulmonary manifestations of sepsis. Treatment to counteract these mediators might make it possible to improve the prognosis of this condition and increase patient survival. One current hypothesis suggests that removal of these mediators from the circulation by plasmapheresis would be of clinical benefit.

A theoretical basis for the removal of these pathologic mediators by extracorporeal methods can be found in several animal studies. Polymyxin B is known to have antiendotoxin properties. After infusing rates with endotoxin, Cohen et al[25] performed plasmapheresis using a solid phase polymyxin B adsorption column in some animals, while other animals did not undergo plasmapheresis. Animals treated with adsorption column plasmapheresis were protected from endotoxin-associated leukopenia, thrombocytopenia, and death. Decreased plasma endotoxin levels were found in the animals who underwent plasmapheresis, and endotoxin was recovered from the adsorption columns.[25] Hanaswa et al[58] also utilized a polymyxin B immobilized fiber hemoperfusion column to detoxify endotoxin in dogs infused with endotoxin or *Escherichia coli.* Hemoperfusion with the polymyxin B column resulted in an increased survival rate in both the endotoxin and *E. coli* infused animals. Gomez et al[48] found that hemofiltration improved left ventricular function in dogs made septic by *E. coli* infusion.

Although extracorporeal methods have been used in the treatment of some critically ill patients with sepsis, few studies have assessed the results in a meaningful way. Most of these involve small numbers of patients and lack controls.[11, 50, 166] Serum from burn patients and thermally injured animals contains factors that interfere with cellular function and contribute to refractory burn shock. Plasmapheresis has been attempted in the treatment of refractory burn shock; however, a clear role for its use has not been established.[112, 167] Plasmapheresis also has been employed in meningococcal sepsis[14] and septic cholangitis.[4] In a small series of patients with multisystem failure, the use of continuous arteriovenous plasmafiltration combined with dialysis resulted in a decreased mortality rate in comparison with treatment with either hemodialysis or continuous arteriovenous hemofiltration.[11] These preliminary results are provocative and potentially exciting, revealing the need for additional studies of this emerging technology.

Extracorporeal Support of Ventilation

The adult respiratory distress syndrome (ARDS) is associated with a high mortality rate. This factor combined with experimental evidence that presently available methods of ventilation may contribute to the lung damage of this syndrome[35, 88] has lead to the trial of newer methods of ventilation in patients with ARDS. Extracorporeal membrane oxygenation (ECMO) and low-frequency positive-pressure ventilation with extracorporeal CO_2 removal (LFPPV-ECO_2R) have both been employed in therapy for ARDS.

The National Institutes of Health ECMO Trial published in 1979 compared a control group of patients with severe acute respiratory failure who received standard mechanical ventilation with an experimental group who received standard mechanical ventilation supplemented with partial venoarterial bypass and membrane oxygenation. The venoarterial bypass procedure utilized a roller pump and decreased pulmonary blood flow from 3.5 to 2.4 L per minute. The patients receiving ECMO had decreased platelet counts, decreased white blood cell concentrations, and received greater infusions of blood and plasma. From days 2 to 11, patients receiving ECMO had a slightly higher survival rate. After day 11, the survival rates for the two groups were the same: 9.5% in the bypass group versus 8.3% in the control group.[170] In contrast to these relatively negative results in adult patients, ECMO has achieved more success in newborns with respiratory distress syndrome. Survival rates of 54 to 85% have been reported.[10]

Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal dissociates oxygen uptake from CO_2 removal. Carbon dioxide is removed via a venovenous extracorporeal circuit with a blood flow rate one-fourth to one-third of total cardiac output. Oxygen is supplied during near apneic ventilation, with only three to five breaths delivered per minute to maintain functional residual capacity. This maneuver permits the lungs to rest. Resting the lung has a theoretical basis in experimental studies, which suggest that traditional positive-pressure ventilation may contribute to the lung injury of ARDS. Gattinoni et al[42] used LFPPV-ECO_2R in 43 patients with severe acute respiratory failure. The expected mortality rate in these patients was greater than 90% based on data from historical controls. In the reported studies, lung function improved in 31 patients (72.8%), and 21 patients (48.6%) survived. The benefit to lung function was generally seen within 48 hours of starting treatment. Mean time on bypass was 5.4 ± 3.5 days.[42] The investigators speculated that the observed improvement in survival in their study in comparison with that in the ECMO trial might have related to important differences in technique. Venovenous bypass might have had a less adverse effect on pulmonary hemodynamics in comparison with the venoarterial bypass used in the ECMO trial, e.g., reduced blood flow might have decreased the likelihood of lung repair.[89] To resolve the important questions that have been posed by these preliminary data, an extensive clinical trial using different forms of ventilation including LFPPV-ECO_2R for ARDS is presently being conducted.[114]

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Metabolic Support in Severe Cardiopulmonary Insufficiency

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Patients with cardiac and pulmonary insufficiency constitute a major percentage of admissions to the intensive care unit. Considerable evidence exists that malnutrition is associated with and can exacerbate both syndromes. In the last 25 years, the technological ability to administer nutritional therapy has grown enormously; in the same period, the realization that complex interrelationships exist between nutrition and metabolism in various disease states also has developed. In this review, the metabolic support of patients with severe cardiac and pulmonary insufficiency is discussed. In addition to reviewing the consequences of both malnutrition and nutritional support in such patients, we present recent data suggesting that pharmacologic effects of nutrients have major implications for patients with severe respiratory and cardiac failure.

PULMONARY INSUFFICIENCY

Metabolic Aspects of the Respiratory System

Restriction of protein and calorie intake results in abnormalities in the control of ventilation and respiratory muscle function; it also causes pulmonary structural changes and deterioration of pulmonary defense mechanisms. These phenomena occur in patients without underlying lung disease, but have more serious consequences in patients with significant pulmonary dysfunction. Short-term food deprivation influences lung metabolism and biochemistry; prolonged partial food restriction affects lung structure and mechanics as well.

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Pulmonary Parenchyma and Surfactant

Studies in animals have repeatedly shown that lung weight is decreased in both short-term fasting and starvation. Food deprivation in rats is associated with proportional reductions in both wet and dry lung weights that are less severe than the loss of body weight.[97] Loss of connective tissue proteins and fat is the most likely cause of these changes.[95] The lungs of starved rats contain less absolute volume of air compared with those of fed rats and demonstrate a decrease in elastic recoil pressure during inflation and deflation.[97] On this basis, it was hypothesized that changes in surface forces were related to loss of surfactant, and that alterations in tissue elasticity were most likely a result of decreased connective tissue components. The mechanism responsible for surfactant deficiency in food-deprived animals is not clear. Lung weights as well as surface forces returned to normal levels after 1 week of refeeding.[96]

Pulmonary Defense Mechanisms

The effects of protein-calorie malnutrition on the immune system are most profound on cell-mediated immunity.[67] The humoral immune system also may be affected.[110] This influence of malnutrition on immunity has a direct impact on alveolar defenses. Alveolar phagocytic function as well as the clearance of various microorganisms are impaired. Clinical studies have shown a marked increase in respiratory infections in malnourished children.[104] Nutritional impairment reduces tracheal cell adherance and increases the frequency of bacterial colonization.[79] This may precipitate nosocomial lung infections and sepsis.

Respiratory Muscles: Metabolism and Function

The diaphragm is a skeletal muscle subject to the demand of continuous work. Diaphragmatic fatigue, both acute and chronic, can be a serious clinical problem associated with extreme physical effort, respiratory diseases, and malnutrition.

Diaphragmatic substrate utilization depends on the intensity and duration of exercise. At low work levels, blood glucose, and lactate and fatty acids are the main fuel sources. The rate of glucose utilization is chiefly regulated by the fatty acid concentration in the bloodstream; increased oxidation of fatty acids has inhibitory effects on the transportation of glucose and on the enzymes of the glycolytic pathway (hexokinase, 6-phosphofructokinase, and pyruvatedehydrokinase). With prolonged exercise, fatty acids become increasingly important, whereas during high intensities of work, the stores of muscle glycogen primarily limit performance.[10] The release of lactate is insignificant below the highest work rates and the involvement of fast twitch glycolytic motor units. The reason for low glycogenolysis has been attributed to the high level of citric acid cycle enzymes and the high mitochondrial density in the diaphragmatic muscle cells. The diaphragm consists of both oxidative and glycolytic fibers and, thus, simultaneous production and utilization of lactate can occur.[55] During hypoxic exercise, circulating epinephrine mediates the conversion of glycogen phosphorylase to an active form with the resultant stimulation of glycogenolysis.

The oxygen requirements of the working diaphragm are satisfied preferentially by augmented blood flow within the muscle. In an animal study, perfusion of the diaphragm was reported to increase fivefold in response to incremental respiratory work.[87] In spontaneously breathing septic dogs, diaphragmatic blood flow contributed 20% of cardiac output, indicating that diaphragmatic perfusion is sustained at the expense of other organs. With mechanical ventilation (elimination of respiratory work), this proportion can be reduced remarkably.[49] Hormonal factors, such as circulating catecholamines, may be involved in the modulation of the resistance of blood vessels.

The development of intracellular acidosis due to the accumulation of hydrogen ions (H^+) has been suggested as a causative factor of muscle fatigue. Acidosis inhibits the activity of glycolytic enzymes (phosphofructokinase) and may block the Ca^{2+}-dependent excitation-contraction action. In addition, H^+ may directly reduce the binding of actin and myosin molecules. A high correlation has been observed between intracellular acidosis and the declining force of diaphragmatic preparation in vitro.[69] Increased perfusion may thus prevent accumulation of H^+ and permit the diaphragm to sustain higher contractile effort. The biochemical basis for chronic fatique is still unknown. Several attempts have been made to relieve diaphragmatic fatique by nutritional and pharmacologic interventions, such as branched chain amino acids, ketone bodies, medium-chain triglycerides, and glutamate or methyl xanthines, but the benefits of these interventions are for the most part highly questionable.[74] Indeed, some evidence suggests that branched chain amino acids may have positive effects on diaphragmatic function.

The respiratory muscles are subject to the same catabolic conditions as other skeletal muscles during starvation and stress.[89] The diaphragm, the principal muscle of respiration, is often used to exemplify the entire respiratory system. The relationship between malnutrition and the respiratory system has been studied widely by Rochester.[89] They found that for a body weight loss of 32%, the corresponding loss of diaphragm was 43%.[5] This respiratory muscle weight loss was associated with loss of respiratory muscle strength, vital capacity, and maximum voluntary ventilation.[6] In the Minnesota Starvation Study of Keys et al,[56] the subjects lost 24% of their body weight in 24 weeks and showed a simultaneous progressive decline in vital capacity. Vital capacity returned to normal values after 12 weeks of refeeding. Similar relations between body weight and respiratory function have been observed in patients with anorexia nervosa.[26] Kelly et al[54] found a positive relationship between inspiratory muscle strength and body cell mass in surgical patients requiring nutritional support.

The impairment in respiratory muscle function exceeds the loss of muscle mass.[32] This suggests that diaphragmatic pressure is reduced in part because there is less muscle, but also because the remaining muscle is weaker. Malnourished patients undergoing nutritional repletion have been found to have improved muscle strength within 2 weeks, long before lean body mass is completely restored.[121] The changes in muscle function seem to be biphasic. Initially, a rapid restoration of biochemical functions occurs that results in functional improvement.[94] This is followed by a period of repletion of actual muscle tissue. The latter is a slow process necessitating 1 to several weeks to obtain significant results.[89]

Respiratory Drive

Doekel et al[29] found that clinical semistarvation in normal volunteers for 10 days reduced the ventilatory response to hypoxia by 42%. Refeeding returned hypoxic drive to baseline. Weissman et al[117], using mean inspiratory flow as an index of neuromuscular drive, noted a 26% decrease in ventilatory drive after 7 days of hypocaloric glucose, indicating that starvation affects ventilation. Refeeding with amino acids restored the depressed ventilatory drive.

Nutritional Aspects of Mechanical Ventilation

A body weight of less than 80% of ideal has been noted in 24% of patients admitted to the intensive care unit with acute respiratory failure.[86] Patients with malnutrition who required mechanical ventilation had a higher mortality than well-nourished patients on mechanical ventilation.[31] Progressive malnutrition frequently occurs in mechanically ventilated patients despite an initially normal body weight. Findings from several retrospective studies suggest that successful weaning from mechanical ventilation can be facilitated by appropriate nutritional support.[16, 62] Bassili and Deitel[16] reported that 90% of patients who received hyperalimentation were weaned from mechanical ventilation compared with 55% who received only intravenous fluids.

Metabolic Substrate Support and the Respiratory System

Administration of nutrients can improve respiratory muscle function, defense mechanisms, and whole body metabolic status. Nutritional substrates can also interfere with the respiratory system through their physiologic and pharmacologic properties: increasing carbohydrate intake increases ventilatory demand because of increased CO_2 production, lipids may alter pulmonary vascular tone and the inflammatory response as precursors for eicosanoid production, and amino acids may increase oxygen consumption and stimulate ventilation by altering respiratory drive. It is important to keep these interactions in mind when nutritional programs are designed for patients with pulmonary conditions.

Carbohydrates. Nutritional intake influences respiratory function through alterations in metabolic demand, with changes in respiratory quotient (RQ) and ventilatory drive. Due to the increased CO_2 production, increasing glucose intake is a stimulus to ventilation. Numerous researchers have reported an increase in CO_2 production and RQ with the administration of hypertonic glucose.[7, 25] As substrates shift from fat oxidation to glucose oxidation, an increase in RQ occurs; if sufficient glucose is given, lipogenesis occurs, with a dramatic rise in the level of CO_2 production. A small patient may double his or her CO_2 production, from 500 kcal per day to 3000 kcal per day of glucose-based total parenteral nutrition. In normal subjects, such an increase in minute ventilation has no noticeable effect on breathing. In patients with impaired lung function, however, this can lead to respiratory distress.[7, 25] The weaning from mechanical ventilation may be more difficult during administration of total parenteral nutrition when glucose is administered as the only nonprotein caloric source.[10]

Lipids. Substitution of fat emulsions for nonprotein calories lowers the RQ, reducing minute ventilation and ventilatory demand.[37] Intravenous fat emulsions (IVFE) are therefore a useful substrate for providing nutritional support in the patient with reduced pulmonary reserve.

Numerous studies have suggested varying degrees of apparent pulmonary dysfunction when IVFE are given. The changes are of interest in understanding the interaction between IVFE and the lung but are generally not of sufficient magnitude to carry much clinical significance. The lung dysfunction generally consists of a decrease in PaO_2 and has been attributed to the associated hyperlipemia.[37] However, recent studies, indicate that the decrease in PaO_2 is due to ventilation/perfusion inequalities caused by an IVFE-related increase in eicosanoid production that causes alterations in the pulmonary vasomotor tone.[42] The polyunsaturated fatty acids in the IVFE serve as precursors of the eicosanoids. Experimental studies in animals have documented that IVFE infusions change eicosanoid serum levels.[42] These alterations seem to be responsible for the changes in pulmonary function, because indomethacin (a cyclooxygenase inhibitor) has been found to prevent the IVFE-related changes in pulmonary function.[41] Due to the varied effects of the different eicosanoids, IVFE have physiologic actions on the lung. These effects may in fact be beneficial to patients suffering from some pulmonary diseases. In some patients with cystic fibrosis, we have noticed a thinning of secretions, fewer pulmonary infections, and an overall clinical improvement after long-term total parenteral nutrition.[8, 106] We have suggested that this may due to a pharmacologic anti-inflammatory effect of the fat emulsion mediated via eicosanoid synthesis.[107]

Infusion of fat emulsions has a mixed action on the pulmonary vascular bed. When given as a bolus or rapid infusion, a vasoconstrictive response is reported; when IVFE is given as a slow infusion, a vasodilating effect is seen. The reason for these results is unclear, but it has been suggested that they also are caused by an alteration in eicosanoid production because the response is blocked by indomethacin.[41, 42] In a study of adults, both healthy volunteers and ventilator-dependent critically ill patients, Jarnberg et al[53] found no significant changes in values for blood gases and diffusing capacity during infusion of a 20% fat emulsion. In patients with mechanical ventilation, Venus et al[116] observed an elevation in mean pulmonary artery pressure and in Q_s/Q_t when Intralipid (Kabi-Vitrium, Stockholm, Sweden) was infused over a period of 8 to 10 hours. The values returned to normal after cessation of the infusion. The infusion also was associated with a significant decrease in the PaO_2/FIO_2 ratio. In a follow-up study on mechanically ventilated patients without sepsis admitted to the intensive care unit, the effects of rate of infusion on gas exchange parameters and central hemodynamics were tested.[58] When 500 mL of 20% Intralipid was given over 24 hours, no effects on Q_{va}/Q_t or MPAP were found. If the same amount was infused over 6 hours, these parameters increased significantly. Fat emulsion should not be abandoned in critically ill patients, but rapid infusions should be avoided and adequate oxygenation verified in patients with compromised pulmonary function who are receiving IVFE.

In addition to the rate of infusion, the effects of IVFE appear to be dependent on the duration of the infusion and the content of polyunsaturated fatty acid in the IVFE. Because the eicosanoids formed locally in the lung in response to lipid infusion are not stored, the effects are not likely to be sustained after the cessation of the infusion. In experimental lung models, pulmonary vasomotor tone returned to baseline values 45 to 120 minutes after the IVFE infusion.[42] The content of fatty acids also determines the effect on eicosanoid synthesis. Several epidemiologic, experimental, and clinical studies have reported a dampening of inflammation when the n-3 fatty acids are enriched relative to the n-6 family in the diet.[115] This is explained in part by production of the "3-series" of prostaglandins formed from the n-3 fatty acids. By modulating the content of polyunsaturated fatty acids in the IVFE, it may be possible to influence the effect of the IVFE on immunologic response and vasomotor tone and other eicosanoid-mediated effects on the lung.

Proteins. Administration of total parenteral nutrition consisting of glucose and amino acids has been shown to cause abrupt increases in minute ventilation. The increase in minute ventilation may result in respiratory distress in patients with compromised pulmonary function.[7] The increased ventilatory demand has been ascribed to increases in CO_2 production. However, some of the total parenteral nutrition-induced increase in ventilation is actually due to the amino acids.[9, 117] Weissman et al[117] semistarved eight normal subjects with an infusion of 5% dextrose for 7 days followed by an infusion of 3.5% amino acids for 24 hours. During the period of semistarvation, a decrease occurred in inspiratory flow. Infusion of amino acids caused a rise in both resting minute ventilation and ventilatory drive, as well as in the ventilatory response to CO_2. Askanazi et al[9] studied the ventilatory response to protein intake in malnourished patients and reported that when the amino acid component of a fixed caloric intake was increased, minute ventilation increased and $PaCO_2$ decreased. An enhanced ventilatory response to a CO_2 stimulus, seen as a leftward shift of the minute ventilation to $PaCO_2$ regression, was found with increased protein intake (Fig. 1). The effect was believed to be due for the most part to increased ventilatory chemosensitivity to CO_2.

Recent studies by Takala et al[111] demonstrate that the effects of amino acids on respiration are a function of the amino acid profile of the infusion. When a 4-hour infusion of an amino acid solution enriched with the branch chain amino acids (leucine, isoleucine, and valine) was compared with that of a standard amino acid solution in healthy subjects, both solutions increased minute ventilation and mean inspiratory flow. However, only the branch chain amino acid infusion caused a significant decrease in $PaCO_2$ and an increase in the ventilatory response to CO_2 inhalation. Infusion of branch chain amino acids also has effects on respiratory in the myocardium as glycogen and lipids. No single fuel is ideal for the myocardium under all conditions. Any of the fuels that may be desirable and preferentially utilized under some conditions can become undesirable under other conditions. The extent to which these varying fuels are used has important implications for myocardial function and the tissue damage that occurs to the myocardium in stressed states.

Glucose metabolism generally occurs along two pathways: glycolysis and oxidative phosphorylation. The latter process includes the citric acid cycle and the electron transport system. Glycolysis produces a relatively small amount of ATP as compared with oxidative phosphorylation (Fig. 2). However, because glycolysis can proceed anaerobically, it becomes a significant factor in energy production during anoxia and hypoxic conditions. Approximately 20% of myocardial oxygen consumption by the resting aerobic heart is accounted for by the oxidation of glucose; approximately 1% of the ATP synthesis occurs in the passage of these glucose residues through the glycolytic pathway.

Glucose transport into the cardiac cell occurs via a carrier-mediated facilitated diffusion process that does not require energy. In the absence of insulin, glucose transport into the cell is the rate-limiting step for glucose utilization by heart muscle. The hexokinase reaction, the first step of intracellular glucose processing, becomes rate limiting if transport is stimulated by insulin and free glucose accumulates in the cell.[72] Increased cardiac pressure work increases the rate of glucose utilization, primarily via a stimulation of transport.[18, 75] Glucose utilization in the myocardium is inhibited by the presence of high circulating levels of alternate substrates, such as free fatty acids or ketone bodies, partly through an inhibition of glucose transport.[76] Oxidation of fatty acids inhibits glucose transport when transport is stimulated by insulin or increased cardiac pressure work.[78] The presence of palmitate in plasma does not inhibit glucose transport in anaerobic hearts, which suggests that the free fatty acids must be oxidized before the transport is inhibited. A decrease in oxidative metabolism accelerates glucose transport into the myocardium (Table 1).[72]

Lipid fuels are available as free fatty acids, ketones, triglycerides, and lipoproteins (Fig. 2). The last two fuels may be broken down to free fatty acids by membrane-bound lipoprotein lipase. Under normal resting conditions, lipid fuels provide as much as 70% to 80% of oxidative metabolism in the myocardium.[93, 122] Plasma free fatty acids are the primary source of fat for oxidation, whereas fatty acids from plasma triglycerides or lipoproteins have only a small role. In the normal resting heart, free fatty acids are utilized in preference to carbohydrate.[21]

The utilization of lipids by the heart is influenced by several factors. It has long been recognized that plasma levels of individual free fatty acids are very important in determining the myocardial uptake of the substrate.[93] The utilization is also a function of the availability of alternate competing substrates, primarily glucose.[76, 122] At a constant rate of energy utilization, an increased supply of free fatty acids has only a limited ability to accelerate fatty acid uptake. However, increased cardiac pressure work will increase fatty acid oxidation at any constant level of fatty acids.[21, 78]

The oxidation of free fatty acids by the heart sharply declines with a decrease in oxygen supply.[81] Fatty acid uptake may continue, but a large fraction will be converted to serum lipids. High intracellular free fatty acids concentrations may have detrimental effects on myocardial function; very high free fatty acids concentrations increase the rate of myocardial oxygen consumption,[71] and in patients with ischemic heart disease, high free fatty acids concentrations have been associated with arrhythmias.[80, 108] In isolated rat hearts and in the dog heart, abnormally high free fatty acids concentrations result in decreased myocardial contractility[44] and arrhythmias.[61]

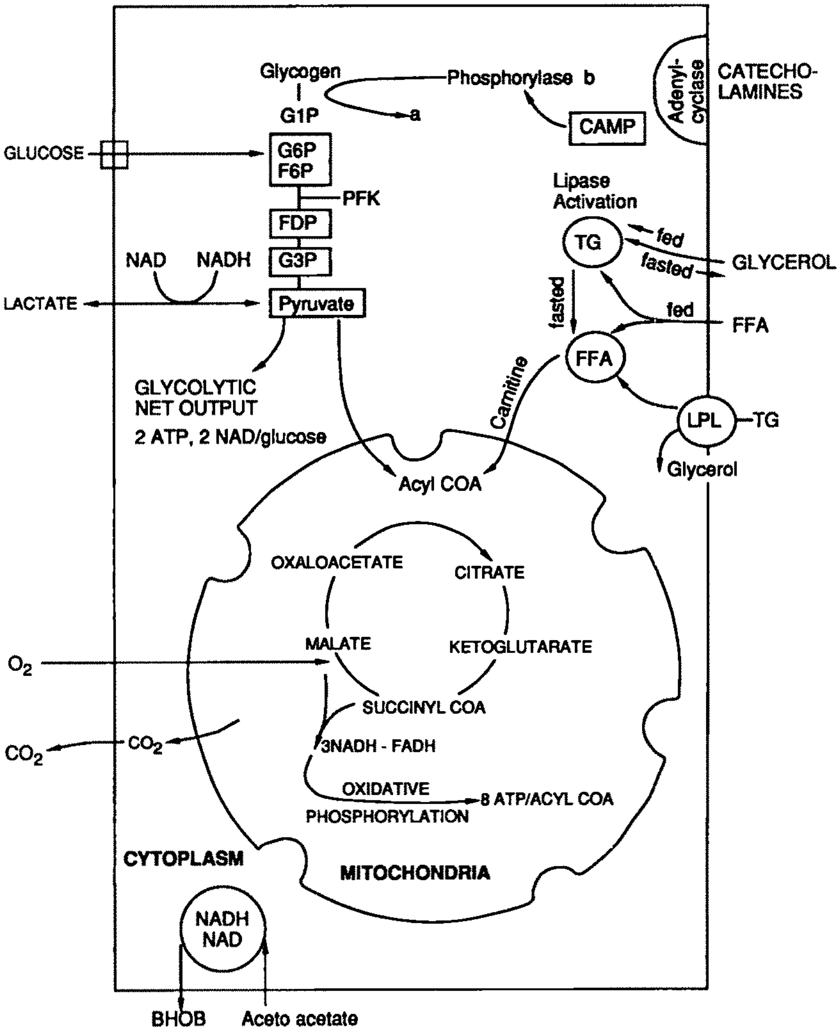

Figure 2. Fuel metabolism in the normal heart. The pathways for energy generation from fat and glucose are illustrated. The primary fuel is the circulating free fatty acid (FFA). Glucose can be obtained from circulating glucose or myocardial glycogen stores. Under anaerobic conditions, lactate is present in high concentrations in plasma and is oxidized as the primary energy source by the myocardium. (*From* Askanazi J, Van deWiele B, Rosenbaum SH, et al: Nutrition and cardiac function. *In* Kaplan J (ed): Cardiac Anesthesia. Grune & Stratton, New York, 1987, pp 1077–1102; with permission.)

Free fatty acids and glucose are believed to be the preferred exogenous substrates for oxidative metabolism in the normal myocardium. Recent studies have suggested that myocardial utilization of these substrates may be impaired after ischemia and cardioplegia.[70] The myocardium may circumvent these abnormalities in lipid and glucose metabolism by using another substance for oxidative metabolism. When the normal dog heart is given the choice between lactate, glucose, or fat, lactate is the preferred substrate.[30, 52] As seen in Figure 3, with increasing arterial concentration of lactate, there is continued extraction by the heart for energy

Table 1. *Glucose Transport in Heart Muscle*

CHARACTERISTICS AND REGULATION OF GLUCOSE TRANSPORT INTO THE CARDIAC CELL
Does not require energy
Is stimulated by insulin
Is the rate-limiting step in glucose utilization in the absence of insulin
Increased cardiac pressure work facilitates transport
Hypoxia and anoxia augment transport
Fatty-acid oxidation inhibits glucose transport

utilization. This occurs in the presence of high concentrations of glucose and free fatty acids. The cardiac metabolism is high in relation to its blood flow as reflected in the large difference in oxygen content between arterial and coronary sinus blood. The increased myocardial requirement for oxygen and energy substrates during physical work seems to be covered mainly by increased coronary blood flow. The extraction of free fatty acids and glucose has been found to be unchanged during work, whereas an increased extraction of lactate in proportion to the higher arterial level at work has been observed.[21] Lactate enters the citric acid cycle by conversion to pyruvate and has been found to be the preferred substrate for oxidative metabolism when lactate concentrations are elevated.[30, 52] Normally, the circulating levels of free fatty acid are fairly constant, whereas the lactate level is very low (approximately 1 mmol/L). At this low resting level, total extraction of lactate by the heart would not provide sufficient energy. However, if the lactate level is raised, as during exercise and septic shock, the myocardial lactate utilization rises.[28, 30] With moderate exercise, the arterial lactate level rises to 5.0 mmol/L due to lactate discharged from the working skeletal muscles. This lactate can be used for

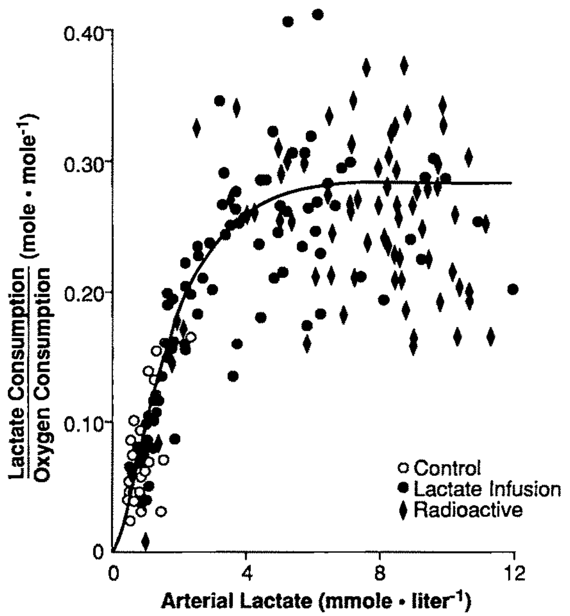

Figure 3. Uptake of lactate as a function of arterial concentration. (*From* Drake AJ, Haines JR, Nobel MIM, et al: Preferential uptake of lactate by the normal myocardium in dogs. Cardiovasc Res 14:65–72, 1980; with permission.)

immediate energy production in the heart. Lactate levels rise to 12.0 mmol/L or more during severe exercise. Experimental studies have shown that the extraction rate of lactate reaches a plateau at a point when arterial lactate exceeds 4.5 mmol/L.[30] At that point, lactate supplies almost 90% of myocardial energy needs. Recent studies have suggested that the myocardial utilization of fat and glucose may be impaired after cardioplegia and ischemia.[70] Increasing arterial concentrations of lactate may improve myocardial and functional recovery. Teoh et al[112] gave exogenous lactate supplementation and found that lactate was the preferred substrate for the myocardium after cardioplegic arrest, and that high circulating lactate levels were followed by improved myocardial metabolic and functional recovery with a reduced perioperative ischemic injury.

Effects of Ischemia and Hypoxia on Cardiac Metabolism

Oxygen deficiency (ischemia) in the myocardium is most commonly induced by a reduction in coronary flow. In contrast to hypoxia or anoxia, in which the flow of blood is maintained with low or no oxygen tension, ischemia leads to the accumulation of products that further modify biochemical reactions. During cardiac ischemia and hypoxia, the amount of oxygen available to support oxidation by the citric acid cycle is reduced. Fatty acids are diverted from β-oxidation to deposition as tissue triglycerides.[120] High levels of free fatty acids may produce detrimental clinical effects, such as increases in myocardial oxygen consumption, myocardial depression, and arrhythmias.[44, 61, 71, 80, 108]

Ischemia leads almost immediately to a manifold increase in glucose transport and in glycolysis. The glycolytic ATP production, however, is not sufficient to maintain normal tissue concentrations of high-energy phosphate. Tissue levels of citric acid cycle intermediates decrease during ischemia, and the pyruvate formed is diverted to lactate.[85] The metabolic alterations responsible for the activation of glucose utilization during anaerobic metabolism include enhanced glucose transport and hexokinase and phosphofructokinase enzyme activity[85] as well as an increased glycogen breakdown. The rate of glycolysis drops after approximately 3 minutes, probably due to the inhibition of phosphofructokinase by lactic acidosis.[85]

Experimentally, ischemia and hypoxia result in different metabolic responses. In general, hypoxia accelerates consumption of glucose to a greater extent than ischemia.[59] This may be due to a greater accumulation of metabolites with ischemia than with hypoxia. Patterns of regulation of glycolysis in hypoxia are not necessarily the same as the much more complex situation in developing infarction; the rate of coronary flow as well as collateral blood supply reaching the oxygen-limited heart appears to be crucial in determining the metabolic response of the myocardial tissue.

Ischemia leads to a deterioration in left ventricular function. Covell et al[24] found that after 1 minute of ischemia, left ventricular function deteriorated, whereas the level of ATP was still normal. Neely et al[77] observed that after 12 minutes, 75% of control levels of ATP existed, whereas left ventricular function had deteriorated completely. This suggests that much of the ATP may not be available for contraction or that the contractile process is inhibited by accumulation of toxic metabolites during ischemia.

Protein Synthesis and Degradation

The myocardium can either reduce or enlarge its chamber volume and muscle mass according to the applied metabolic and hemodynamic workload. The heart is not spared during periods of protein loss that occur in starvation and stress.[1, 56] The belief that the myocardium is spared during catabolic stress because cardiac muscle is actively working while limb skeletal muscle is immobile is invalid. These losses are restored during periods of repletion.

When the myofibrillar wall tension is chronically augmented because of an increase in either intraventricular pressure or chamber volume, the myocardium responds by myofibrillar growth that has the net effect of normalizing the wall tension.[39] The metabolic signals involved in the enhanced protein synthesis occurring during a metabolic or hemodynamic workload include circulating fuels and hormonal substances.[123] The exact physiologic role of these factors is unknown. The turnover of cardiac proteins is a fairly rapid process. Insulin, thyroid, and growth hormone may have direct trophic effects on the heart. Protein synthesis and degradation are both energy-dependent processes and could be modified to varying degrees by hypoxia or ischemia. Accumulation of lactate and hydrogen ions also may be factors that account for the inhibition of protein degradation in ischemic muscle.

Metabolic Substrate Support in Cardiac Failure

Glucose-Insulin-Potassium. Glucose-insulin-potassium (GIK) solutions have metabolic effects that may be beneficial for the function of the heart. The theoretical rationale behind GIK treatment is manifold: raising the blood glucose level should increase the rate of glucose utilization; an elevated insulin level should stimulate transport of glucose as well as stabilize cell membranes; and the addition of potassium should compensate for its loss from the myocardium during hypoxia and ischemia. Potassium loss reduces the rate of glycolysis due to the dependence of the kinase enzymes on K^+ ions for maximal activity. GIK infusion also depresses circulating levels of free fatty acids,[109] which are liberated under stressful situations. Under experimental conditions of hypoxia, infusions of free fatty acid depress the contractility of the heart[44, 45, 59] and elevate myocardial oxygen consumption.[59] Studies measuring blood flow and arterial-coronary sinus differences during GIK infusion under stable clinical conditions have shown an increased myocardial glucose utilization accompanied by a reduction in free fatty acid utilization.[90] A change in myocardial respiratory quotient occurred, indicating a change from lipid to carbohydrate metabolism.

Experimental studies have demonstrated protective effects of glucose and insulin on the ischemic myocardium as indicated by improved contractile function, augmented myocardial ATP provision, and the preservation of function and structure of hypoxic myocardium.[4, 43] Infusion of GIK during experimental acute coronary occlusion reduced the predicted size of myocardial infarctions.[64] Infusion of GIK into the baboon with experimental infarction resulted in preservation of histologic appearance, structural anatomy, ionic concentration, and phosphorylated compounds in the myocardium.[82]

The clinical trials in which GIK has been administered to patients with ischemic heart disease have been inconclusive and are clouded by the differences in the concentrations of the solutions, rate, and duration of infusion as well as patient selection. Rogers et al[66, 91, 92, 118] compared patients given GIK with patients treated in a standard manner for acute myocardial infarction. The GIK solution (300 g glucose, 50 units of insulin, and 80 mmol KCl per liter H_2O) was given via the atrial lumen of a pulmonary artery catheter at the rate of 1.5 mL/kg/hour for 48 hours. The control group received 0.5 N saline solution. A lower number of premature ventricular contractions occurred and episodes of ventricular tachycardia were lower, with less requirement for lidocaine, in the patients receiving the 48-hour period of GIK infusion than in the control patients.[91] Values of pulmonary artery end-diastolic pressure and cardiac index returned to the normal range in a significantly greater number of patients receiving GIK than in the control subjects.[118] When radionuclide techniques for estimating left ventricular function were performed, GIK recipients showed improved global ventricular function and improved segmental function of the infarcted myocardium.[66, 118]

Studies have suggested a reduction in the myocardial scar during the first days of acute infarction as well as 3 weeks postinfarction. Estimates of infarct size in which enzyme analysis has been used have not demonstrated a difference between GIK recipients and control patients.[91] However, radionuclide studies do suggest reduced infarct size because GIK solutions increased global ejection fraction, increased ejection fraction in the infarct zone, and decreased pulmonary arterial end-diastolic pressure and end-systolic and diastolic volumes (Fig. 4).[118] Angiocardiographic quantification of segmental wall motion 3 weeks after infarction showed that the segmental area of contraction was larger in patients receiving GIK than in control patients.[40] Satler et al[98] reported an improved ventricular function and reduced size of segmental wall motion abnormality in patients with infarctions who received a 48-hour infusion of GIK.

Rogers et al[92] reported a decreased mortality in GIK recipients. Hospital mortality for the control group was 29.7% and for the GIK group, 15.7%. A study by Dennis et al[27] indicated that during stress states (e.g., the postoperative period or trauma), GIK improved myocardial performance as evidenced by higher cardiac output at any given filling pressure.

Despite the reported effects of GIK infusion during acute myocardial infarction, the therapeutic use of GIK has not gained wide acceptance, partly because of the potential for significant complications after infusion. Meticulous attention to serum levels of glucose and potassium is necessary during and immediately following discontinuation of GIK. Pulmonary ingestion, phlebitis, and hypoglycemia are not infrequent complications of this therapy.[27] The last two complications are related to the presence of potassium and insulin in the solution. Martinez and Jewitt[65] infused hypertonic glucose (a bolus of 10 g followed by infusion of a 30% glucose solution at a constant rate of 10 mg/kg/min) in patients with coronary artery disease. They found that infusion of glucose alone produced metabolic changes similar to those

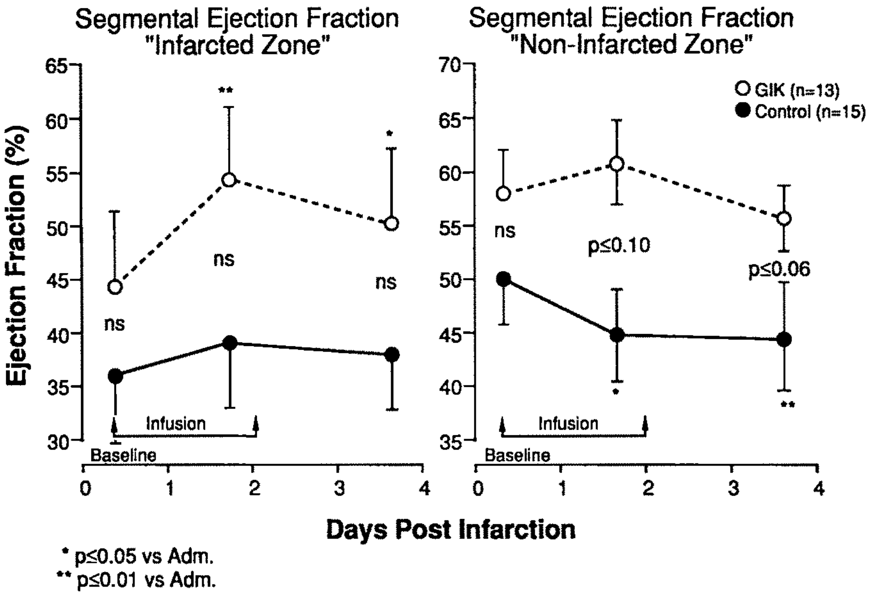

Figure 4. Segmental ejection fraction versus days after myocardial infarction for the infarcted zone *(left)* and noninfarcted zone *(right)*. (*From* Whitlow PL, Rogers WJ, Smith LR, et al: Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. Am J Cardiol 49:811–820, 1982; with permission.)

observed during infusion of GIK. Infusion of hypertonic glucose solution during infarction should have no detrimental hemodynamic effects and fewer side effects.

Carnitine. Adequate cardiac levels of carnitine are necessary for mitochondrial transmembrane transport of free fatty acids. Carnitine is an essential cofactor for the oxidative metabolism of long-chain fatty acids. It transports long-chain fatty acids from the cytosol into the mitochondrial matrix sites of β-oxidation.

It has been suggested that carnitine supplementation may be of value to the myocardium under ischemic, stressed conditions. Its beneficial effects would be prevention of the high intracellular concentration of free fatty acids because of their binding with carnitine. Hypoxia and ischemia deplete free carnitine from myocardium.[105] Administration of L-carnitine restores free L-carnitine levels in myocardium to nearly normal levels.[84] Several experimental animal studies have supported the function of carnitine as being protective to the ischemic, stressed myocardium, and carnitine administration has been found to diminish cardiac cell injury produced by ischemia.[20, 33, 34] Thompson et al[113] demonstrated improved pacing tolerance of the ischemic heart in humans after supplementation with carnitine.

A deficiency of myocardial carnitine has been proposed as an etiologic factor in cardiomyopathia. Animal models have demonstrated that myocardial carnitine stores are markedly reduced in dilated and hypertrophic forms of cardiomyopathy.[19] Supplemental carnitine has been shown to improve left ventricular function in cardiomyopathic animals.[119]

Although carnitine administration may improve free fatty acid utilization and myocardial performance, its routine clinical use must await further studies on efficacy and safety.

Lactate. Lactate has been shown to be the preferred substrate for the heart. As much as 90% of myocardial energy needs can be provided by lactic acid, with a plateau occurring at 4.5 mmol/L. Lactate also may be the preferred substrate in clinical conditions such as septic shock and postcardiac bypass state (see section on fuel substrate utilization).

Taurine. Taurine is the most abundant free amino acid in the mammalian heart.[50] It has been reported to have various effects on the cardiovascular system, including inotropic, antiarrythmic, and hypotensive action.[51] The inotropic action of taurine has been demonstrated in various heart preparations.[36, 100] The effect is independent of catecholamine stores or β-adrenergic receptor sites because β-adrenergic blockade does not alter the inotropic response of the isolated perfused heart to taurine.[99] Clinical studies have verified that administration of taurine has an inotropic effect and improves depressed hemodynamic variables and cardiac performance in patients with congestive heart failure.[13, 14] Taurine also has been reported to reduce cardiac arrhythmias induced by toxic doses of digoxin and adrenaline.[88]

Most inotropic agents appear to affect contractility by making more calcium available to the myofilaments. Evidence is accumulating that taurine is involved in the regulation of calcium homeostasis by controlling the calcium movement through myocardial sarcolemma. The cardiotonic actions may be exerted through modulation of the high binding sites on the myocardial sarcolemma.[103] Taurine also has been found to promote the formation of vasodilator and antiaggregating PGI_2 at the expense of vasoconstrictor and proaggregating TXA_2.[22] This may be a factor in the defense of myocardium against anoxia and ischemia. Taurine's inotropic and antiarrythmic effects are promising. It differs from most synthetic compounds with calcium ion entry-blocking properties in that taurine does not exert a cardiodepressant activity. However, important questions still remain regarding its biochemical mechanisms of action and clinical usefulness.

Branch Chain Amino Acids. The role of branch chain amino acids in the regulation of cardiac protein metabolism was demonstrated when protein synthesis in perfused hearts was stimulated by these entities. This stimulatory action was primarily due to leucine, which also inhibited protein degradation.[23] However, the effect of leucine on protein synthesis could not be demonstrated in working hearts supplied with insulin and energy substrates nor in intact rats.[68] The beneficial effect of branch chain amino acids, particularly leucine, on protein turnover can only occur under special conditions in which catabolism is sufficiently enhanced, because no acute effects of branch chain amino acid administration on muscle protein turnover were observed in cardiac patients with muscle wasting ("cardiac cachexia").[73]

Some experimental studies have indicated a protective effect of branch chain amino acids on the ischemic myocardium. Branch chain amino acids may conserve ATP during ischemia; they significantly delayed the onset of ischemic contracture and the postischemic recovery of pressure in perfused rat hearts after global ischemia.[102] The presence of a branch chain amino-acids–enriched formula and glucose in the cardioplegic solution enhanced myocardial protection during global ischemia in the energy-depleted rat heart.[101] The branch chain amino acids may be utilized by cardiac muscles as an energy source and, thus, may improve postischemic myocardial function when given before cardiac surgery or during reperfusion, as would occur in myocardial infarction with reperfusion occuring either spontaneously or by coronary thrombolysis or angioplasty.

Other Substrate Support. Other metabolic interventions may be of use in patients with cardiac deficits. Amino acid compounds, such as glutamate, aspartate, arginine, malate, succinate, and fumarate, have been shown experimentally to enhance myocardial energy production and to improve mechanical recovery in the anoxic and ischemic heart.[3] The effects of an intravenous infusion of mixed essential and nonessential amino acids in a canine heart preparation are mildly positive.[3] There are no data reporting the specific inotropic effects of the individual amino acids, such as those found in the amino acid infusion that has been tested to date. Theoretically, some of the glucogenic amino acids, such as alanine, might be directly converted to energy sources for immediate myocardial utilization, and the positive inotropic effect observed would be similar to that seen with the use of glucose infusions.

Effects of Metabolic Support on the Cardiovascular System

The metabolic and cardiovascular profile of fasting changes with food ingestion. Within 30 minutes after food intake, thermogenesis rises to peak at 30 to 60 minutes and then gradually declines over the next few hours.[15] This thermic effect of food results in increased VO_2, VCO_2, minute ventilation (V_E), heart rate, stroke volume, myocardial oxygen consumption (MVO_2), and systolic blood pressure, accompanied by a fall in systemic vascular resistance (SVR). Left ventricular filling pressure and diastolic blood pressure are usually unchanged (Fig. 5).[15]

The specific mechanisms involved in the physiologic changes associated with nutrient intake are uncertain. The actions involved in chewing, digesting, and absorbing food are considered to have a minor role. The rise in cardiac output is due to increased mesenteric blood flow associated with food ingestion and a rise in whole body oxygen consumption.[15] Currently, it is believed that the metabolic response is largely related to processing and storage of nutrients.

Continuous infusion eliminates the physiologic swings seen in bolus infusions. With either continuous nasogastric or intravenous nutrition, the patient remains in a constant intraprandial state. When continuous infusions remain at a constant rate, resting VO_2, VCO_2, metabolic rate, V_E, heart rate, blood pressure, cardiac output, and SVR remain steady throughout the day and change only during physical activity and sleep.[46]

Three factors determine the metabolic, respiratory, and cardiovascular response

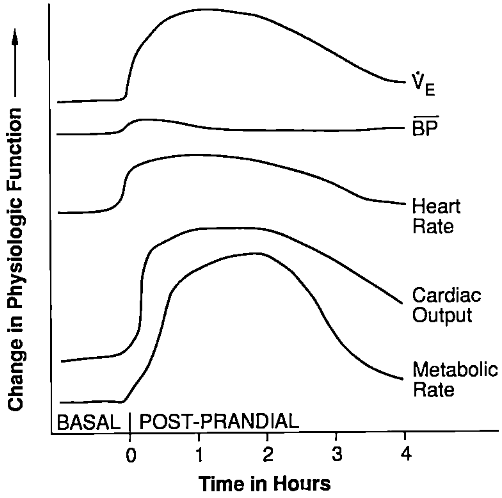

Figure 5. Graphic representation of the changes in various physiologic functions after ingestion of a meal. (*From* Heymsfield SB, Erbland M, Casper K, et al: Enteral nutritional support. Metabolic, cardiovascular, and pulmonary interrelations. Clin Chest Med 7:41–67, 1986; with permission.)

to continuous feeding: the rate of energy infusion, the composition of the energy source, and the disease state. As the flow rate of enteral formulas is increased from fasting to maintenance level, little or no change is observed in resting energy level and VO_2.[47] Increasing the infusion rate above maintenance energy requirements results in a rise in resting energy level with associated cardiac and respiratory changes (Fig. 6). High infusion rates, in general, increase the RQ in a fashion related to the formula infused. This is most likely due to lipogenesis. In terms of cardiovascular demands, the increases in VO_2 and heart rate seen with increasing infusion rate above the maintenance level are relatively small. However, in patients with severe cardiac failure with limited cardiac reserve, this may be of clinical importance.

In stressed states, such as after major trauma, there is a catabolic phase of injury. When continuous hyperalimentation is given to patients in a stressed state, a marked rise is detected in VO_2 and VCO_2.[10] The implication from the cardiovascular perspective is that the hemodynamic response to hyperalimentation may be more marked in a patient suffering from a major injury than in the nonstressed patient.

The two main categories of diet composition are high-carbohydrate and normal or high-fat preparations. When the energy infusion rate is increased above maintenance, VCO_2 and V_E increase more rapidly with administration of high-carbohydrate formula in comparison with high-fat solutions.[48] Protein is the most thermogenic substrate. The effect is not always obvious; changing from standard to protein-free formula causes negative nitrogen balance but no appreciable change in metabolic rate and cardiac output.[35] This indicates that protein, per se, is not responsible for the metabolic and cardiovascular effects of continuous energy infusion.

The cardiovascular effects of lipid are not well understood. Ingestion of a fatty meal may precipitate angina, which is promptly reversible with the administration of heparin, which activates lipoprotein lipase.[10] Postprandial angina due to ingestion of a fatty meal differs from that caused by a mixed caloric composition meal.[60] It occurs some 3 hours after ingestion and is not associated with the increase in left ventricular filling pressure and drop in stroke volume that can be seen after ingestion of a mixed fuel.

Infusion of fat emulsions produces negative inotropic effects and reduces SVR in a canine isovolumetric preparation.[38] An increased incidence of arrhythmias in ischemic dogs during infusion of IVFE has been reported. Pacold et al[83] showed that IVFE infusion in patients with stable coronary artery disease results in a

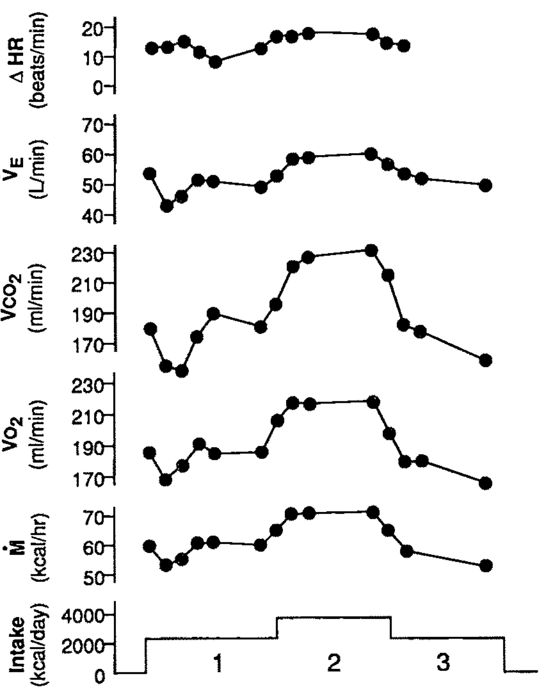

Figure 6. Changes in physiologic indices when continuous nasoenteral feeding was increased from near-zero balance (period 1) into the repletional range (period 2). In the third period formula, infusion rate was returned to the period 1 level. Each infusion lasted 1 week. HR = changes in resting heart rate from fasting; M = resting metabolic rate. (*From* Heymsfield SB, Hoff RD, Gray TF, et al: Cardiac diseases. *In* Kinney JM, Jeejeebhoy KN, Hill GL, et al (eds): Nutrition and Metabolism in Patient Care. Philadelphia, W.B. Saunders Company, 1988, pp 477–509; with permission.)

reduction in nuclear left ventricular ejection fraction. No clinical or cardiographic signs of ischemia were noted, and the change was reversible with heparin-induced decrease in free fatty acids. Abel et al[2] studied patients who had had coronary artery bypass graft surgery and observed a significant decrease in cardiac output associated with an increase in pulmonary capillary wedge pressure with the administration of IVFE at a rate of 2 mL/min (1440 mL/12 hours). No significant hemodynamic changes were demonstrated at an infusion rate of 1 mL/min. Transient sinus bradycardia has been observed.[114] It is likely that an effect on coronary vasomotion exists, however, this has not yet been defined. The fatty acid profile as well as the rate and dose of fat infused may have a role in its cardiac effects. Medium-chain triglycerides are not dependent on carnitine for oxidation and may perhaps be of advantage.

SUMMARY

Numerous investigators have demonstrated that a progressive weight loss is associated with advancing cardiopulmonary insufficiency. The loss of body mass influences cardiopulmonary metabolism and biochemistry as well as the structure and mechanics of the myocardium and the lung. Weight loss becomes not only a common occurence but a serious risk. Nutritional and metabolic substrate support should therefore be considered strongly in these patients. However, the nutrients themselves exert complex effects on the hemodynamic and respiratory system; they may have profound physiologic and pharmacologic actions aside from an improvement in whole body metabolic and nutritional status. It is therefore important to consider these interactions when setting up programs for nutritional support.

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Critical Care of the Immunocompromised Patient

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RESPIRATORY FAILURE

Respiratory failure is a common cause of intensive care unit admission in immunocompromised patients and is one of the most common causes of death. Although infection is the most frequently diagnosed cause of respiratory decompensation,[68, 89] the actual pathologic entity is often never determined. Thus, management is usually empiric and must include broad-spectrum antibiotics and antifungal agents because infections can be rapidly fatal in the immunocompromised host.

Initial management of respiratory failure does not differ in immunocompromised patients; prompt attention should be given to establishing an airway and providing adequate oxygenation. As soon as the patient is stabilized, the past medical history, stage as well as past and present treatment of the underlying malignancy, current immunologic status, antibiotic treatment, hematologic profile, and prognosis must be reviewed to formulate a meaningful differential diagnosis and realistic treatment plan.

Infection as a Cause of Respiratory Failure

Immunocompromised patients are vulnerable to a wide variety of infections due to the derangement of immune defenses caused by the underlying diseases (lymphomas, aplastic anemia,[5] lung cancer,[70] leukemia, acquired immunodeficiency syndrome [AIDS]); therapy-related neutropenia and immunosuppression; exposure to blood products; exposure to hospital flora and broad-spectrum antibiotics; and disruption of bodily defenses through malnutrition, operation, mucosal inflammation, and long-term indwelling vascular devices. Thus, infection should be included in the differential diagnosis for any immunocompromised patient with respiratory failure, even when clinical signs of sepsis (fever, changes on radiographs of the chest, alteration of the white blood cell count, sputum production, and so forth) are not obvious.

Neutropenia. Neutropenia is common in acute leukemia, aplastic anemia, and after chemotherapy or radiotherapy. Neutropenic patients who present with fever

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and an abnormal chest radiograph most likely have a bacterial pneumonia, despite the absence of sputum.[62, 93] The most common organisms infecting untreated, nonhospitalized neutropenic patients are *Streptococcus pneumoniae, Hemophilus influenzae, Mycoplasma pneumoniae,* and *Staphylococcus aureus.*[60]

After chemotherapy for hematologic malignancies, neutropenia is often prolonged. Bouts of fever in these patients may be caused by infection with unusual organisms, hospital flora, or strains resistant to previously administered antibiotics. Broad-spectrum antibiotic therapy should be initiated immediately if respiratory function deteriorates in these patients. Infection by organisms not sensitive to the current regimen should be suspected, and the therapy should be empirically changed to cover bacteria most commonly associated with severe pneumonia in the neutropenic hospitalized patient, such as *Klebsiella pneumoniae, Enterobacter cloacae, Escherichia coli, Proteus* species, *Serratia marcescens,* and *Staphylococcus* and *Streptococcus* species.[60] Viral agents and fungi, including *Candida* and *Aspergillus,* should be considered as well; indeed, the risk of respiratory failure from infection with *Aspergillus fumigatus* increases with the duration of neutropenia, administration of broad-spectrum antibiotics, and the presence of hematologic malignancies.[43, 106]

Patients with solid tumors may receive chemotherapy for advanced disease. As a result, they also are at risk for severe opportunistic infections. However, the degree and duration of bone marrow suppression from chemotherapy is usually less than that seen after treatment of hematologic malignancies.

Defective Cell-Mediated Immunity. Cell-mediated immunity is defective in acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, lymphomas, and AIDS. Although these patients are affected by the usual community-acquired bacterial, viral, and atypical pneumonias, they also are at greatly increased risk for infections with *Listeria monocytogenes, Salmonella,* mycobacteria, *Nocardia asteroides,* and *Legionella pneumophila.* Mycobacteria tuberculosis infection in this group is usually due to reactivation of a previous infection. Fulminant respiratory failure from infection with *Nocardia*[39] and far less commonly with *Cryptococcus, Histoplasma,* and *Coccidiomycoses* has been reported.[74] Viruses, particularly cytomegalovirus, and parasites (*Pneumocystis carinii, Toxoplasma gondii, Cryptosporidium, Strongyloides stercoralis*) also are important pulmonary pathogens in this population.

Defective Humoral Immunity. Humoral immunity, relatively well preserved in acute leukemias, is diminished in patients with AIDS, chronic lymphocytic leukemia, multiple myeloma, or agammaglobulinemia and in those receiving steroids, all of whom are more susceptible to infection with encapsulated organisms, such as *S. pneumoniae, H. influenzae,* and the *Neisseria* species. The infection usually appears first at a sinopulmonary site in contrast to infection with these same organisms in the splenectomized patient, which often presents as bacteremia or septicemia.[74]

Steroids. The administration of steroids is common in chemotherapy for Hodgkin's disease, acute lymphocytic leukemia, AIDS-related tumors, and non-Hodgkin lymphomas, as well as for treatment of central nervous system and bony metastatic disease from solid tumors. This form of therapy carries a high risk of reactivating latent infections, such as with *Mycobacterium tuberculosis.* Of great concern is the risk of developing *P. carinii* pneumonia during corticosteroid therapy, which also is postulated to be due to reactivation of a latent infection. Other organisms that may infect the patient who is receiving steroids include *Listeria, Salmonella,* fungi, and viruses.[47]

Splenectomy. Splenectomy is performed for staging and in therapy for certain malignant conditions, such as lymphomas, chronic lymphocytic leukemia, chronic myelocytic leukemia, and hairy-cell leukemia. These patients are at risk of developing serious infection with encapsulated organisms. These infections frequently present with bacteremia, which may rapidly progress to systemic sepsis.

Transfusion. Immunocompromised patients frequently require transfusion of blood products during chemotherapy or extensive operative resections. The infectious complications of transfusions are primarily viral and are potentially devastating to the immunosuppressed host. The risk of developing transfusion-related cytomegalovirus infection is increased in states of compromised immunity.[1] Consequently, the incidence of cytomegalovirus pneumonitis is elevated in patients infected with the human immunodeficiency virus, those receiving chemotherapy for leukemia, and those who have undergone a bone marrow transplant.

Bone Marrow Transplantation. After allogeneic bone marrow transplantation, the differential diagnosis of respiratory failure due to infectious agents is broad and is a function of the antigenic status of both the marrow donor and recipient, as well as the length of time since the transplant and the degree and duration of neutropenia. The pretransplant conditioning regimen, which may include high-dose cyclophosphamide or total body irradiation or both, also is important when an attempt is made to determine the causative organisms.

In patients who have received a bone marrow transplant, interstitial pneumonitis may develop, with progressive respiratory failure, within the first 3 months after the transplant. These patients are frequently febrile, with diffuse pulmonary infiltrates on radiography of the chest. The isolation of specific organisms from sputum or even open lung biopsy is rare, even though several infectious agents have been implicated. These include viral agents, primarily cytomegalovirus,[23] and other opportunistic organisms. In the presence of graft-versus-host disease, idiopathic interstitial pneumonitis accounts for two out of three deaths after a bone marrow transplant.[104]

Twenty percent of patients who undergo bone marrow transplant die of viral lung injury, cytomegalovirus being the most frequently isolated organism. Other agents include respiratory syncytial virus, adenovirus, parainfluenza, and influenza virus. The existence of specific antiviral therapies (ribavirin, ganciclovir, acyclovir) mandates a vigorous search for these pathogens.

Sepsis. In any immunocompromised patient, generalized sepsis with hypotension is more likely to inflict injury on a lung already damaged by chemotherapy or radiation. The clinical presentation of adult respiratory distress syndrome (ARDS) in this group is the same as in any other critically ill population, with bilateral infiltrates on radiography of the chest and progressive respiratory failure.

Pulmonary Hemorrhage as a Cause of Respiratory Failure

Hemorrhage due to thrombocytopenia, coagulopathy, and vascular destruction by tumor or infectious agents occurs in immunocompromised patients.[28] Pulmonary hemorrhage is not always associated with hemoptysis because the bleeding may only take place in the pulmonary interstitium. In such patients, a high index of suspicion is required to reach a diagnosis, administer supportive management, and correct the coagulopathy. The diagnosis may be retrospective when dyspnea and new infiltrates develop suddenly in a thrombocytopenic patient and improve more rapidly than would be expected if an infectious process were the cause.

Patients with platelet counts less than 20,000 mm^3 may experience spontaneous pulmonary hemorrhage even in the absence of clinically evident tissue pathology. Bleeding may occur with a higher platelet count with pre-existing intrathoracic pathology, such as interstitial pneumonitis or endobronchial lesions. Patients in whom invasive aspergillosis, or other infectious processes with a tendency to invade blood vessels, develops may present with hemoptysis. Endobronchial tumors or erosion into a bronchus from interstitial tumors (e.g., epidermoid carcinoma) can cause hemoptysis.

Many immunocompromised patients with respiratory failure have risk factors for pulmonary hemorrhage, and, therefore, this diagnosis should be considered seriously even in the absence of hemoptysis.

Pulmonary Injuries Secondary to the Treatment of Malignancies

Pulmonary toxicity from chemotherapy and radiotherapy is well described. Many cytotoxic agents alone or in combination are known to cause acute, subacute, and chronic injury to lung tissue, at times leading to respiratory failure.

Dose-related toxicity occurs with many agents, whereas hypersensitivity pneumonitis can be precipitated by the administration of others (Table 1).

The clinical manifestations of toxicity from these agents is varied. Drug-induced pneumonitis can have an insidious onset, with progressive dyspnea, dry cough, and, finally, cyanosis. These symptoms occur during or 1 to 3 months after chemotherapy. Progressive respiratory failure is usually irreversible when caused by cyclophosphamide; other agents, such as methotrexate, produce reversible syndromes.[56]

Noncardiogenic pulmonary edema has been attributed to many chemotherapeutic agents as well as to the biologic response modifiers (Table 1). This syndrome is characterized by the rapid onset of respiratory distress, with frothy sputum production and chest tightness. Mitomycin C also may produce hemorrhagic pulmonary edema during therapy or even months later.[56]

Slowly progressive dyspnea, with production of thick white sputum, has been seen in patients secondary to pulmonary alveolar proteinosis after busulfan administration. Cyclosporin A also has been linked to pulmonary alveolar proteinosis, with acute respiratory failure, cardiovascular collapse, and death.[56]

Chest-pain syndromes mimicking pleuritis or myocardial infarction or both have been reported with bleomycin,[102] cyclophosphamide,[35] and methotrexate.[92]

The chemotherapy and radiotherapy conditioning regimen of bone marrow transplantation as well as other unknown factors have produced syndromes of obstructive pulmonary disease, interstitial pneumonitis, and bronchiolitis obliterans. A progressive decrease in diffusing capacity has been observed over time, which is often asymptomatic but can progress to respiratory failure.[15, 73, 100]

Some agents without inherent pulmonary toxicity have been shown to produce respiratory failure when combined with other agents. The vinca alkaloids, which alone are only rarely implicated in respiratory failure, produced respiratory failure in seven patients when combined with mitomycin C.[56] Likewise, nitrosoureas when combined with cyclophosphamide produce toxicity at lower doses than when administered alone. Cis-platinum, which is excreted renally, can theoretically increase the risk of bleomycin-induced pneumonitis by interfering with its excretion, unpredictably raising blood levels of bleomycin.

Table 1. *Chemotherapeutic Agents Associated with Pulmonary Toxicity*

Dose-related toxicity[56]	Noncardiogenic pulmonary edema[24, 56]
Bleomycin	Bleomycin
Busulfan	Cyclophosphamide
Carmustine	Cytarabine
Chlorambucil	GM-CSF
Lomustine[54]	Ifosfamide
Hypersensitivity reactions[56]	Interleukin-2
Bleomycin	Methotrexate
Cyclophosphamide	Mitomycin-C
Methotrexate	
Mitomycin-C	
Procarbazine	

Radiotherapy of the thorax is associated with pneumonitis when doses exceed than 18 to 20 Gy. High-dose cyclophosphamide, part of the conditioning regimen for bone marrow transplantation, exacerbates radiation pneumonitis at lower radiation doses. Other agents that potentiate the effect of radiation on the lungs include anthracyclines, bleomycin, busulfan, and nitrosoureas. This effect is most pronounced when the drugs are administered simultaneously with the radiation and are less pronounced when the treatments are sequential.

Pulmonary toxicity of the combination of oxygen and bleomycin is well described.[54] The effect can be seen as long as 12 months after bleomycin administration. Oxygen also may amplify the toxic effect of carmustine, cyclophosphamide, and mitomycin.

Tumor Progression as a Cause of Respiratory Failure

Lymphangitic spread of malignancy and diffuse parenchymal metastases can appear clinically and radiologically similar to pulmonary hemorrhage, infection, or ARDS. In addition, hemorrhage and infection can obscure the diagnosis of metastases to the lung.[9]

Cardiac Disease Producing Respiratory Failure

Respiratory decompensation may be cardiogenic in origin. Exposure to cardiotoxic drugs, radiotherapy, and infectious agents increases the risk of cardiac dysfunction in immunocompromised patients. The administration of large volumes of fluid (blood products, antibiotics, and parenteral nutrition) necessary to support these patients further stresses the dysfunctional heart. Echocardiography and pulmonary artery catheters are often necessary to determine whether there is a cardiogenic component to respiratory failure.

Other Causes of Respiratory Failure

In addition to those causes of respiratory failure to which the immunocompromised patient is particularly vulnerable, other common causes of respiratory decompensation should be considered. These include pulmonary emboli, for which patients with malignancies are at high risk[57]; postoperative respiratory failure in patients with borderline preoperative pulmonary function; post-thoracotomy infection producing bronchopleural fistula or empyema, which is seen more commonly in patients who have received preoperative radiotherapy[66]; respiratory tract obstruction from mediastinal or intrathoracic tumors; and aspiration pneumonitis, which is seen in patients with head and neck tumors or esophageal lesions causing swallowing dysfunction and in patients with altered levels of consciousness.

Diagnosis and Management

After stabilization of the patient with supplemental oxygen, continuous positive airway pressure face mask, or mechanical ventilation, a detailed history of preexisting cardiopulmonary disease should be obtained. Medical records should be reviewed to determine previous courses of chemotherapy and radiotherapy received and the extent of tumor at the last evaluation. A review of the current medications, including antibiotics, and the results of any microbiologic investigations is essential. Attempts to narrow the differential diagnosis in this population are difficult, and treatment will often be supportive and empiric.

Clinical examination and noninvasive tests frequently have a low diagnostic yield. Fever is common, even in the absence of infection. Sputum is infrequently produced, even in the presence of infection, and is frequently colonized and contaminated with organisms when obtained by cough or through the endotracheal tube. The findings on chest radiography are nonspecific in many instances but are useful to rule out pneumothorax or lobar collapse. Noninvasive cardiac evaluation with electrocardiography and echocardiography can identify a cardiogenic contribution to respiratory failure; however, precordial echocardiography can be difficult to perform on mechanically ventilated patients with high levels of positive end-expiratory pressure. Invasive hemodynamic monitoring with a pulmonary artery catheter is useful and can and should be performed in most patients, with platelet infusion during the catheter insertion, if necessary.

Invasive diagnostic procedures, such as bronchoscopy with transbronchial biopsy or open lung biopsy, may be indicated if the management would be altered by the findings. These methods to diagnose respiratory failure can have great risk, especially in thrombocytopenic and neutropenic patients. However, in many patients, the benefits may outweigh the risk.

Bronchoscopy can be performed, usually after endotracheal intubation, in most immunocompromised patients unless they require high levels of positive end-expiratory pressure. In these patients, the risk-benefit ratio may not justify the use of bronchoscopy, because patients often experience severe prolonged arterial desaturation secondary to alveolar collapse after the procedure. Empiric treatment of all diseases that could be identified by bronchoscopy may be the most prudent approach to management.

Bronchoalveolar lavage is safe in neutropenic and thrombocytopenic individuals and has a reasonable yield for most opportunistic infections and some malignancies.[87, 88] However, it cannot distinguish colonization from tissue invasion by fungi, and specimens may be contaminated with oropharyngeal flora. Use of newer techniques, such as telescoping plugged catheters, and quantitative lavage cultures may increase the yield of bronchoalveolar lavage.[29, 105]

Transbronchial biopsy is rarely possible in the critically ill immunocompromised patient because mechanical ventilation and thrombocytopenia increase the risk of bleeding from this procedure. Open lung biopsy may then be required to diagnose the cause of focal lesions[22] or when drug-related pulmonary toxicity is suspected. Its utility may be limited, however, as shown in a study of 28 leukemic patients[31] in which a definitive diagnosis was rarely established by open lung biopsy.

Management of respiratory failure in the immunocompromised patient requires broad coverage of infectious causes of pulmonary disease, including viral, parasitic, and fungal agents in certain populations; attention to hemodynamic, fluid, and hematologic status of the patient; and knowledge of the effects of chemotherapy, radiation, operation, and immunotherapy on the lung.

CARDIOVASCULAR DISORDERS

The causes of cardiovascular instability in immunocompromised patients differ from the causes in other critical care settings. Immunocompromised patients are more prone to sepsis, bleeding, and thrombosis as a consequence of their underlying malignant conditions or the treatment of these diseases. Immunocompromised patients have been exposed to many agents with arrhythmogenic potential and acute or chronic effects on the myocardium. Pericardial disease is common, producing chest pain, arrhythmias, and tamponade.

Arrhythmias

Supraventricular arrhythmias are more common in the cancer patient than are ventricular arrhythmias.[69] The causes of supraventricular arrhythmias in patients with cancer include pericarditis; pulmonary disease, including pulmonary emboli; drug effects, seen with interleukin-2,[24] interferon,[18, 24] doxorubicin,[25] and 5-fluorouracil;[65] and metabolic derangements.

Pericarditis occurs frequently in immunocompromised patients and can produce arrhythmias, particularly when associated with myocarditis.[72] The causes of pericarditis in immunocompromised patients include radiotherapy, which most commonly produces an effusive pericarditis within 12 months of therapy[6, 45, 72]; infection (with enterovirus, pyogenic bacteria, mycobacteria, and fungi); and chemotherapeutic agents, most commonly cyclophosphamide and doxorubicin.

Pericardial involvement with malignancy is common with metastatic disease from the lung (15%–35% of patients have pericardial involvement),[66] breast, and malignant melanoma. Infiltration of the pericardium can occur with lymphoma and leukemia.

The diagnosis of pericardial effusions or involvement by tumor can be accomplished by precordial echocardiography. In some critically ill patients, an adequate precordial echocardiogram cannot be obtained because of the placement of surgical wound dressings and drains or because of hyperinflation of the lungs by emphysema or positive end-expiratory pressure. In these patients, transesophageal echocardiography can be performed while oxygen saturation and hemodynamic status are monitored. In patients who are thrombocytopenic, transesophageal echocardiography has been safely performed while platelets are infused.

Other causes of arrhythmias in the immunocompromised patient include metabolic derangements, such as hypokalemia and hypomagnesemia, seen frequently with amphotericin therapy and cis-platin administration. Hypocalcemia, seen in acute tumor lysis syndrome, can increase susceptibility to ventricular dysrhythmias. Invasion of the myocardium and the conducting system has been reported with leukemia and melanoma, producing primarily supraventricular arrhythmias.

The management of arrhythmias in this patient group does not differ from that in any other group. A 12-lead electrocardiogram should be obtained to rule out ischemia and to characterize the arrhythmia; electrolyte disorders should be corrected; and the position of intracardiac catheters should be checked. Arrhythmias associated with cardiac instability should be cardioverted. If pericarditis is diagnosed, pharmacologic antiarrhythmic therapy should be instituted while the inflammation and underlying cause are treated.

The management of drug-induced arrhythmias depends on the drug. Arrhythmias associated with interferon therapy have been treated successfully with antiarrhythmic therapy while the interferon therapy continued.[18] Interleukin-2-associated arrhythmias occur in 14% to 21% of drug recipients; supraventricular arrhythmias can be treated with continuation of the drug. Ventricular tachycardia occurring during interleukin-2 administration necessitates discontinuance of the agent.[24]

Chest-Pain Syndromes and Myocardial Ischemia

The differential diagnosis of chest pain in the immunocompromised patient should include ischemia, pericarditis, pulmonary embolus, pneumonia, and pneumothorax.

Chest pain, associated with dyspnea and electrocardiographic changes consistent with pericarditis, can occur with the administration of bleomycin,[102] cyclophosphamide,[35] and radiotherapy.[6] Methotrexate produces a similar syndrome, usually accompanied by pleuritis.[92] An electrocardiogram and echocardiogram are useful diagnostically. Pericardiocentesis can be helpful; it yielded a diagnosis in 85% of cancer patients with pericardial disease studied at the Dana Farber Cancer Institute.[72]

The symptoms of drug-associated pericarditis often resolve after the drug infusion is stopped. The electrocardiographic changes also can be expected to resolve, although those produced by cyclophosphamide often persist after the effusion is removed, suggesting myocardial involvement.[35]

Chest pain associated with electrocardiographic changes suggestive of myocardial ischemia or infarct has been described with the administration of 5-fluorouracil when given alone or with vindesine.[11, 65] The findings resolve with discontinuance of the drug infusion and the administration of nitrates. They are reproducible with repeat administration of 5-fluorouracil. Acute doxorubicin toxicity produces transient electrocardiographic changes[25] without symptoms. Both interleukin-2 and interferon have been associated with acute myocardial infarction during administration, although these syndromes were frequently reported in patients with pre-existing heart disease.[18, 24]

Because premature coronary artery disease has been found in patients who have undergone radiotherapy for Hodgkin's disease,[6] atherosclerotic cardiovascular disease should be included in the differential diagnosis of suspected myocardial ischemia in younger patients without other risk factors. The clinician should be aware that many immunocompromised patients have the risk factors for ischemic heart disease, particularly those with cigarette-related tumors. On initial evaluation, 10% to 15% of patients with lung cancer have abnormal baseline electrocardiograms.[66]

The management of suspected myocardial ischemia in the immunocompromised patient is the same as in any other patient, with an increased index of suspicion for coronary insufficiency in those patients receiving the previously described agents or mantle radiotherapy, despite the absence of other risk factors. Use of thrombolytic agents in this population carries higher risk than in others, and care should be taken to exclude disseminated intravascular coagulation, coagulopathies, recent surgery, and intracranial lesions before instituting thrombolytic therapy.[38]

Other causes of acute chest pain in this population include pulmonary embolus, which should be suspected strongly in the differential diagnosis given the increased tendency for patients with malignancies to form thrombi.[57] Fungal pneumonia in neutropenic patients caused by infection with *Aspergillus* and *Mucor* can produce chest pain mimicking pulmonary embolus or myocardial infarction.[2] Pneumothorax as a consequence of central line placement or occurring spontaneously in mechanically ventilated patients, in those with pre-existing bullous disease or interstitial pneumonitis,[59] or as a complication of pneumonectomy should always be considered in the evaluation of acute chest pain.

Heart Failure

An immunocompromised patient presenting with acute congestive heart failure should be evaluated with chest radiography, electrocardiography, and echocardiography to rule out ischemia, valvular disease, or diffuse myocardial dysfunction. The management may include diuretics and afterload reduction, with inotropes if appropriate. Specific causes of cardiomyopathy in immunocompromised patients include viral myocarditis (particularly in patients with AIDS),[77] acute cyclophosphamide or doxorubicin toxicity, fungal myocarditis,[98] interferon therapy (rarely),[18] ischemic heart disease, and sepsis.

Shock States

Hypotension in the immunocompromised patient may have many causes, but the most common is sepsis. Immediate treatment with ventilatory and circulatory support with broadening of the antibiotic coverage to cover resistant organisms is essential. Blood cultures should be obtained, although in the neutropenic patient with presumed septic shock, blood cultures are infrequently positive. Known or suspected foci of infection (such as Broviac catheters) should be cultured.

Severe hemorrhage may cause hypotension, particularly in the coagulopathic patient. Hemorrhage into the adrenal glands can also cause hypotension not due to blood loss but to acute adrenal insufficiency. Adrenal insufficiency also should be suspected in a patient who was or is receiving steroid therapy and in patients with

AIDS who may have adrenalitis secondary to direct infection of the organs with cytomegalovirus or the human immunodeficiency virus.

Cardiac function should be assessed early in the treatment of shock, with electrocardiography, echocardiography, and a pulmonary artery catheter. Signs of tamponade should be searched for, particularly in a patient with known malignant pericardial disease and a coagulopathy. Acute valvular disruption, as seen in endocarditis (to which these patients are susceptible), will be evident on echocardiography. Tumor obstruction to the ventricular outflow tract is a theoretical cause of hypotension and has been recognized echocardiographically in patients with extracardiac tumors.[32, 46] Diffuse cardiac dysfunction may suggest myocarditis from drugs, infection, or neoplastic infiltration; however, such an appearance is also common in shock from sepsis[7, 25] or interleukin-2 therapy.[67]

Hemodynamic instability from a massive pulmonary embolism must be ruled out, even in patients with coagulopathy, as completely as possible. The echocardiogram may reveal an enlarged right side of the heart and normal left ventricle that, although suggestive of overload from high pulmonary pressure, is not definitive for pulmonary embolus. A bedside ventilation/perfusion scan may not be helpful because it shows only 30% of the lung; evaluation of a full ventilation/perfusion scan may be hampered by pre-existing pulmonary pathology. Angiography may be impossible if the patient is thrombocytopenic. Fibrinolytic agents should be considered for the patient with hemodynamic instability due to a pulmonary embolus; however, the risks must be considered carefully in this population, as noted earlier.[38]

Hypotension from anaphylaxis after the administration of chemotherapeutic agents[65] can occur (Table 2). Interleukin-2 can produce a shocklike state, with hemodynamic parameters identical to that of sepsis. Capillary leak syndrome with the administration of granulocyte-macrophage colony stimulating factor and interleukin-2 can mimic pulmonary edema with hypotension. Modest blood pressure depression is reported with tumor necrosis factor, granulocyte colony-stimulating factor, and interferon.[24] Most of these syndromes are reversible and respond to fluids; however, fluids may exacerbate the capillary leakage and lead to respiratory compromise.

Pulmonary artery catheters and echocardiography should be used frequently because the myriad shock states in this population are difficult to distinguish clinically.

Table 2. *Chemotherapeutic Agents Associated with Hypotension or Anaphylaxis**

AGENT	SIDE EFFECT
Amsacrine	Anaphylaxis
Asparaginase	Anaphylaxis
Bleomycin	Anaphylaxis
Cis-platin	Anaphylaxis
Cyclophosphamide	Anaphylaxis
Cytarabine	Anaphylaxis
Dacarbazine	Anaphylactoid reaction
Dactinomycin	Anaphylactoid reaction
Daunorubicin	Anaphylactoid reaction
Doxorubicin	Anaphylactoid reaction
Etoposide	Hypotension
Interferon-α	Hypotension
Interleukin-2	Hypotension, capillary leakage
Methotrexate	Anaphylaxis
Mitotane	Hypotension
Tumor necrosis factor	Hypotension, shock

*As reported by Crum[24] and The Medical Letter on Drugs and Therapeutics.[65]

GASTROINTESTINAL TRACT DISORDERS

The gastrointestinal tract is very susceptible to the effects of immunosuppression and its treatment, which occasionally results in bleeding, perforation, obstruction, and liver dysfunction.

Upper Gastrointestinal Bleeding

Bleeding from the upper gastrointestinal tract in immunocompromised patients is often caused by a benign process,[86] such as stress ulceration,[14] esophagitis, gastritis, and peptic ulcer disease, all of which may be exacerbated by treatment-related coagulopathies. Bleeding from malignant involvement of the upper gastrointestinal tract by lymphoma and other tumors can occur, usually after treatment is initiated. Portal hypertension caused by metastatic liver disease producing varices is rare and, thus, an uncommon source of bleeding.[41, 55] Repeated severe episodes of vomiting during chemotherapy increase the likelihood of Mallory-Weiss tears.

The evaluation and definitive diagnosis of bleeding in the upper gastrointestinal tract is best done endoscopically, because a definitive diagnosis will alter the therapy considerably. However, in the immunocompromised patient, endoscopy is often hindered by thrombocytopenia, which increases the risk of biopsy-related bleeding, and neutropenia, which increases the risk of procedure-related bacteremia. An absolute neutrophil count below 500 cells/mm^3 is a relative contraindication to endoscopy.[96]

Initial management of bleeding in the upper gastrointestinal tract in the critically ill immunocompromised patient is supportive, with repletion of blood products, platelets, and clotting factors as needed. Antacids or H-2 blockers in continuous infusion are the mainstay of therapy for acid-related bleeding disorders. However, H-2 blockers may suppress bone marrow and should be avoided in patients after bone marrow transplantation. Specific antiviral, antifungal, or antibacterial therapy for esophagitis promotes healing of the bleeding esophagus.[61, 75, 97] Other causes of bleeding in the upper gastrointestinal tract, such as bleeding tumors, may require surgical management.

Stress ulcer prophylaxis, early treatment of esophagitis, and a good antiemetic regimen are essential in limiting the occurrence of upper gastrointestinal tract bleeding in the critically ill immunocompromised patient.

Lower Gastrointestinal Bleeding

Bleeding from the lower gastrointestinal tract in immunocompromised patients is frequently caused by benign lesions (diverticuli, angiodysplasia), as well as inflammation caused by chemotherapy, radiotherapy, or infection. Intraluminal neoplasms, gastrointestinal lymphoma, ischemia of the gut, and neutropenic enterocolitis (typhlitis) can also produce bleeding. Bowel involvement related to graft-versus-host disease-related can also bleed significantly.

The initial management of lower gastrointestinal tract bleeding includes repletion of blood and volume and attempted correction of any coagulopathy. Radiologic studies of the abdomen should be performed to rule out obstruction and perforation. Ultrasonography can aid in evaluation of typhlitis.[52]

Definitive diagnosis by endoscopy and barium enema frequently must be delayed until the patient is stable enough to tolerate the bowel preparation. In addition, lower endoscopic procedures may be risky in patients with neutropenia and thrombocytopenia, limiting their usefulness.

An intra-abdominal emergency should be suspected in patients receiving high-dose steroids who experience abdominal complaints, because peritoneal signs can be masked by steroid therapy. Although the risk of emergency abdominal surgery in any critically ill immunocompromised patient is high,[34, 90] early surgical consultation is essential because the death rate from perforation of the colon approaches 100% in steroid-treated patients.[3, 76]

Early surgical consultation also is indicated for any patient with an acute abdomen or bleeding tumor or in whom bleeding continues despite medical management.

Obstruction and Ileus

Gastrointestinal tract obstruction can be caused by adhesions produced by prior operation or intraperitoneal chemotherapy,[86] by extraintestinal abdominal or pelvic tumor, or by intraluminal obstruction or intussusception due to primary or metastatic intestinal lesions.[58] Ileus caused by electrolyte derangements and drugs is very common. Pseudo-obstruction has been reported as a paraneoplastic syndrome affecting the myenteric plexus in patients with small cell carcinoma of the lung.[17]

Mechanical obstruction caused by tumor is best assessed by plain films and CT scan. Chemotherapy, radiotherapy, or operation may be used for palliation or cure. Lysis of adhesions is surgically managed. Intussusception, although primarily a malady of children, can be produced by Kaposi's sarcoma and metastases (usually from melanoma) and can be managed surgically with good outcome, even in widespread disease.[58]

Attention to the electrolyte imbalances that cause ileus (hypomagnesemia, hypokalemia) can limit its occurrence; however, the effects of concurrent critical conditions, such as pneumonia, the postoperative state, hypotension/pressors, and the need for drugs such as vincristine, vinblastine, and high-dose cytarabine, make adynamic ileus common and often unavoidable. Ileus is managed by decompression, bowel rest, fluid repletion, and correction of electrolyte derangements.

Oral Mucositis

The oral cavity of the immunocompromised patient is vulnerable to severe inflammation due to infection and the effects of anticancer therapy. Severe mucositis can complicate the management of the critically ill immunocompromised patient by causing pain, exacerbating dehydration and malnutrition, increasing the risk of aspiration, and threatening the airway with mucosal edema and hemorrhage.

In addition to the mechanical problems presented by severe mucositis, alteration in the integrity of the mucosa can predispose the compromised patient to systemic infection[42] and unpredictably increase the absorption of locally applied medications.[4, 20]

Treatment of malignant conditions produces oral complications in 40% to 50% of cancer patients.[26, 50] Direct stomatotoxicity of chemotherapeutic agents is exacerbated by neutropenia and thrombocytopenia, increasing the risk of *Candida* infection and mucosal hemorrhage. Many agents are toxic to the oral mucosa, especially bleomycin, cytarabine, doxorubicin, 5-fluorouracil, and methotrexate.[50]

Radiotherapy to the oral cavity can produce erythema and mucositis after a total dose of 3000 cGy administered over 14 days. Other radiation-related effects include osteonecrosis of the mandible and trismus, both of which can complicate airway management.[78]

Toxicity to the oral mucous membranes after bone marrow transplantation arises from the conditioning regimen, which often includes high-dose chemotherapy and radiation, from infectious agents, and from acute graft-versus-host disease. Oral ulcerations, commonly due to infection with herpes simplex virus, occur 7 to 11 days after a transplant procedure; painful desquamation characteristic of acute graft-versus-host disease is seen approximately 18 days after a transplant procedure.[53]

Acquired immunodeficiency syndrome has numerous oral manifestations, the most common of which is oral candiasis.[27, 81] Hairy leukoplakia, severe periodontal disease, and necrotizing ulcerative gingivitis are also common.[82] The incidence of

Kaposi's sarcoma of the oral cavity is increasing, and this lesion is difficult to treat.[21] Although Kaposi's sarcoma in other areas of the body can be palliated by radiotherapy, the treatment of oral Kaposi's sarcoma is complicated by the occurrence of severe diffuse radiation mucositis at doses lower than expected for normal appearing mucosa. Therapy must frequently be discontinued after only 5 to 7 days and a total radiation dose of 1800 cGy.[21, 99] The cause of this unique sensitivity of normal mucosa surrounding the Kaposi sarcoma is unknown.

The management of severe mucositis generally requires intravenous hydration and nutrition and pain control with local agents or parenteral narcotics. The efficacy of antibacterial rinses in the prophylaxis and treatment of mucositis is equivocal.[30, 85] Once the mucositis is established, patients will benefit from good mouth care. Early consultation with the dental service to construct bite blocks for prevention of maceration of the tongue and buccal mucosa is especially important in the sedated mechanically ventilated patient with severe mucositis.

Esophagitis

Esophagitis in the immunocompromised host can have serious consequences. Esophagitis from all causes can encourage aspiration and can exacerbate the malnourished state frequently seen in immunocompromised patients. Infection with *Candida* organisms is the most common cause of esophagitis in this population and can result in stricture, fistula formation, perforation, bleeding, and dissemination of infection if left untreated.[61] Herpetic esophagitis can also produce these complications but is less commonly a cause of significant hemorrhage.[75] In the past, bacteria found in the esophagus were thought to be contaminants or the result of colonization. However, in the absence of other etiologies, bacterial infection of the esophagus can cause a severe inflammation and has been implicated as a cause of bacteremia in the immunocompromised host.[97]

The radiologic appearance of esophagitis on barium swallow is not sufficient to determine the etiologic agent; diagnosis by endoscopy is the method of choice, with brush biopsy to evaluate tissue invasion. The risks of upper endoscopy and biopsy in the neutropenic, thrombocytopenic host should be kept in mind and balanced against the benefits of early treatment to minimize the complications of esophagitis.

Liver Dysfunction

Liver disease in the immunocompromised patient can present as a subclinical laboratory abnormality, jaundice, or fulminant hepatic failure. The causes are myriad and include toxic effects of many chemotherapeutic agents[65]; infection with cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and other blood-borne agents[48]; vaso-occlusive disease associated with bone marrow transplantation; tumor infiltration and biliary obstruction; or as a consequence of shock.

Malignant biliary obstruction is usually a consequence of local invasion from carcinoma of the pancreas, duodenum, or bile duct and less commonly from metastatic disease to periportal nodes.[86]

Liver metastases can occur with many malignancies, most commonly those from the gastrointestinal tract, lung, breast, and melanoma. The metastases are frequently asymptomatic and only rarely cause fulminant liver failure.[41] Infiltrative diseases, such as leukemia, lymphoma, amyloid secondary to malignancy, and miliary tuberculosis can produce hepatomegaly and liver dysfunction, occasionally accompanied by the development of ascites and portal hypertension. Liver failure without obstruction should raise suspicion of infectious etiologies, such as hepatitis, cytomegalovirus, or Epstein-Barr virus; vaso-occlusive disease, seen primarily in the early period after bone marrow transplantation; or therapy-related hepatotoxicity, seen with chemotherapeutic agents,[65] steroids, or total parenteral nutrition.

The evaluation of liver failure should include ultrasonography and CT.

Endoscopic retrograde cholangiography, if tolerated, is useful to rule out obstruction. Benign processes of obstruction must be sought, with surgical exploration if necessary. A stent may be needed for relief of malignant obstruction while awaiting the outcome of chemotherapy or radiotherapy. Percutaneously placed stents have a theoretical risk of infection, which may make them less appealing in the compromised patient.[8]

Management of liver failure not caused by obstruction includes supportive therapy and discontinuance of known hepatotoxins. The biochemical abnormalities produced by some hepatotoxins, such as total parenteral nutrition, can be expected to resolve within several weeks.

NEUROLOGIC DISORDERS

Although neurologic disturbances are common causes for hospital admission in patients with malignancies,[33] they are uncommon reasons for admission to the critical care unit. However, many critical illnesses in this population are accompanied by alterations in neurologic status, such as diminished level of consciousness, agitation, and seizure activity, which must be evaluated.

Altered Mental Status

In the immunocompromised host, lethargy or other diffuse changes in the level of consciousness should raise a suspicion of early sepsis. Prompt investigation is essential because sepsis can progress rapidly in this population.

Infection of the central nervous system itself is also likely in the patient with compromised immune defenses resulting from the primary disease or chemotherapy (Table 3). These infections result in acute or chronic meningitis, encephalitis, and brain abscess formation.

Acute meningitis in the immunocompromised patient can be caused by bacteria, fungi, protozoa, and viruses. Infection with *Mycobacterium tuberculosis* may be similar clinically to acute meningitis, an unusual presentation in the normal host. The presence of a ventricular shunt or Ommaya reservoir increases the risk for acute central nervous system infection with *Staphylococcus epidermidis.*[91]

Many of the organisms that produce acute meningitis in immunocompromised hosts can also cause a syndrome of chronic meningitis. Patients with lymphoma and leukemia are at risk of developing this syndrome, as are patients with AIDS. The responsible organisms include those described previously, as well as *Mycobacterium avium-intracellulare* and cytomegalovirus. In patients with AIDS, a subacute

Table 3. *Chemotherapeutic Agents Causing Alterations in Mental Status*

AGENT	EFFECT
Aminoglutethemide[65]	Drowsiness
Asparaginase[51]	CNS depression or hyperexcitability
5-fluorouracil[51]	Slurred speech, dizziness
Hexamethylmelamine[51]	Hallucinations, somnolence
Hydroxyurea[65]	Rare somnolence
Ifosfamide[65]	Confusion, hallucinations, coma
Interferon-α[36]	Confusion, disorientation
Methotrexate[51]	Meningismus, lethargy with intrathecal route
Mitotane[65]	CNS depression
Procarbazine[51]	CNS depression
Vincristine[51]	Confusion, delirium, coma

dementia, progressive multifocal leukoencephalopathy is attributed to viral infection with JC virus, a papovavirus, as well as to infection of the brain tissue with the human immunodeficiency virus itself.[95]

Brain abscesses can develop in immunocompromised patients. Bacteremia originating from distant sites of infection may seed the central nervous system hematogenously. Patients with otitis or sinusitis, subacute bacterial endocarditis, or pulmonary infection are at high risk of developing a brain abscess with bacteria and fungi. In patients with AIDS, the simultaneous occurrence of pulmonary infiltrates and a neurologic disorder strongly suggests the possibility of infection with *Aspergillus, Nocardia, Mucor,* and *Candida* organisms.[71]

Other neurologic complications can occur in immunocompromised patients both as a consequence of the primary disease and of its therapy. Thrombocytopenia and coagulation disorders are common in patients with decreased immune function and can precipitate cerebrovascular events.

Narcotics, antiemetics, and steroids are frequently administered to the immunosuppressed patient and can produce changes in mental status. In addition, many chemotherapeutic agents have neurologic side effects (Table 3).

Many of the central nervous system effects of these medications are reversible with discontinuation of the offending drug. However, symptom resolution may be delayed, such as in instances of L-asparaginase encephalopathy, which may take up to 1 week to resolve.[51] Thus, management must often empirically address other etiologies, such as infection, which may not be ruled out even after improvement occurs because a final diagnosis may never be possible.

Seizures

The differential diagnosis for a sudden onset of seizure activity in the immunocompromised patient includes infection, bleeding, metastatic disease, side effects of drug administration or withdrawal, and metabolic derangements, such as hyponatremia, uremia, and hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura.

In a study of 25 patients with solid tumors,[33] the most common causes of seizures were vascular events and brain metastases. In fact, 15 to 30% of metastases in the central nervous system are discovered during evaluation for new seizures.[103] In the human immunodeficiency virus-infected population, a study of 100 patients revealed that a mass lesion, such as an infected abscess or lymphoma, caused approximately one third of new onset seizures. The diagnostic yield in this group was high in patients with a focal interictal examination or status epilepticus.[44]

Some chemotherapeutic agents, such as cis-platin and, less commonly, L-asparaginase and carmustine, can cross the blood-brain barrier and cause seizures. Acute cerebellar degeneration has been produced with 5-fluorouracil[51]; ataxia and dementia develop and can be confused with a seizure disorder.

Management

Evaluation of changes in mental status must include extensive questioning of caretakers to obtain a clear description of the onset of the disorder, a record of medications currently taken or recently discontinued, and to document the occurrence of trauma and any focal signs. The chemotherapy history must also be reviewed thoroughly. Physical examination should include a search for signs of increased intracranial pressure; focal signs suggestive of mass lesion; patchy distribution of neurologic abnormalities suggestive of multiple sites of neuraxis involvement with leptomeningeal metastases; and cutaneous, ocular, oropharyngeal, or pulmonary signs of infection. Laboratory tests should be reviewed, with a focus on abnormalities such as hyponatremia, hypercalcemia, and hypoglycemia. Renal and liver function and the results of microbiologic investigations must also be noted.

The coagulatory function should be assessed frequently, including platelet count, prothrombin time, partial thromboplastin time, and serial DIC screening.

Computed tomography of the head is usually required to rule out intracranial masses or bleeding. Injection of contrast medium is usually necessary to identify leptomeningeal lesions.[103] Magnetic resonance imaging is very useful for identification of lesions in posterior and middle fossae and to determine whether bleeding has occurred within a tumor. However, this test frequently cannot be performed in critically ill patients who may be intubated and need a degree of monitoring that cannot be provided.

Even if infectious meningitis is suspected, lumbar puncture should not be performed in these patients before obtaining a CT scan to rule out mass lesions.

In thrombocytopenic patients, the risk of causing an epidural hematoma by performing lumbar puncture should be weighed against the value of anticipated results. If these results will not change the management of the patient, it is more prudent to forego the procedure and to administer empiric treatment for infection and coagulation disorders. When a lumbar puncture is essential, it should be done with the smallest possible needle and while platelets are infused, if the platelet count is less than 50,000/mm^3. Close observation of all patients, especially those with a low or decreasing platelet count, should continue for at least 24 hours after the procedure. The development of back pain, urinary retention, paraparesis, or sensory loss should immediately raise suspicion of an epidural hematoma. Unfortunately, in many critically ill patients, sedatives, opiates, and indwelling urinary catheters confound the evaluation of cord compression.

Lumbar puncture should be performed whenever neoplastic meningitis or leptomeningeal metastases are suspected because most chemotherapeutic agents do not cross the blood-brain barrier.[83] All patients with leukemia are at increased risk for neoplastic meningitis,[94] whereas leptomeningeal metastases from solid tumors usually occur only with widespread disease.[10] The intracranial pressure may be elevated in leptomeningeal disease. Although the findings of cytologic studies may be negative, a completely normal spinal fluid examination is rare; possible findings may include increased opening pressure, elevated protein, decreased glucose, and increased cell count.[10, 94] Diagnostic yield increases with multiple spinal fluid examinations, and the benefits of this procedure should be weighed against the risk.

Depending on the findings, therapy may include antibiotics or chemotherapeutic agents; placement of a ventricular Ommaya reservoir may be necessary for repeated administration of intrathecal medication. Whole-brain irradiation also may be necessary for treatment of central nervous system disease as well. However, intrathecal chemotherapy, especially with methotrexate, and whole-brain irradiation can cause changes in mental status. Transient somnolence is commonly seen in children who have received 2400 rads of cranial irradiation.[83] A syndrome of aseptic meningitis may occur within hours after the administration of intrathecal methotrexate; usually, this clears spontaneously within 72 hours. When widespread meningeal leukemia is treated with very high-dose intrathecal methotrexate, acute cerebral edema, which responds to steroids, has been reported.[83]

Increased intracranial pressure secondary to metastatic disease can be treated with steroids, preferably dexamethasone (16 mg/day in divided doses), to decrease cerebral edema. This dose will help 70% of patients with symptomatic lesions.[101] If necessary, the dose can be increased to 100 mg/day.[101] Chemotherapy or radiotherapy can be administered concurrently. To avoid a variety of serious complications (e.g., psychosis, infection), steroids should be tapered as soon as possible. Severe intracranial hypertension may require treatment with mannitol, mechanical hyperventilation, and surgical decompression. Anticonvulsants are indicated when seizure activity accompanies mass lesions.[19] Patients receiving steroids may need a higher dose of diphenylhydantoin due to the effect of steroids on hepatic metabolism.

The management of intracranial hemorrhage in this patient population is determined by the underlying cause. Spontaneous hemorrhage due to severe coagulopathy, which is common in leukemic patients, usually occurs intracranially not subdurally. Treatment consists of sedation and administration of platelets and clotting factors and ventilatory support, if necessary.

Nonhemorrhagic infarcts in cancer patients were extensively reviewed by Graus et al.[37] Nonbacterial thrombotic endocarditis was the most common cause of cerebral infarction in this group, followed by intravascular coagulation with a normal cardiac evaluation. Other entities to be considered include septic emboli (usually from *Aspergillus fumigatus*), tumor emboli, and leukemic infiltrates (more common in the myelogenous leukemias).[19]

SUMMARY

Proper critical care management of the immunocompromised patient requires an appreciation of the myriad causes of decompensation in this population, with particular attention to the role of infection. Although the differential diagnosis is often broad, aggressive attempts to narrow the diagnostic possibilities can be very risky in this population. In addition, a delay in initiating treatment caused by these diagnostic maneuvers can be lethal. Thus, the critical care physician who treats immunocompromised patients must be mindful of the spectrum of disorders common to this group and must use this knowledge to formulate and institute a meaningful, if empiric, treatment plan without delay.

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Hepatic and Cardiac Transplantation

*Laurie K. Davies, MD**

LIVER TRANSPLANTATION

The field of hepatic transplantation has undergone rapid expansion since the first human orthotopic liver transplantation was performed by Starzl in 1963. Currently, more than 60 liver transplantation centers exist in the United States.[18] The procedure is being performed more frequently and with greater success than during the pioneering years. Only 28% of an original series of 170 patients treated between 1963 and 1979 survived in comparison with current survival rates of approximately 70% to 80%.[33, 34] The use of liver transplantation expanded rapidly after a Consensus Development Conference of the National Institutes of Health concluded in June 1983 that liver transplantation had become a service and not simply an experimental procedure.[25] With improved survival, the number of indications for liver transplantation is constantly increasing, and patients are being considered for transplantation earlier in the course of their disease before multisystem organ failure intervenes.

The reasons for improved survival in these patients are numerous. One of the primary advances has occurred in the field of immunosuppression, particularly the use of cyclosporine A, a more selective immunosuppressant drug than previous agents. Precise monitoring of cyclosporine blood levels has permitted optimum immunosuppression while minimizing side effects. Liver biopsies are performed more routinely, with earlier recognition of rejection versus infective histologic patterns. Donor liver preservation has markedly improved; the Wisconsin preservation solution has extended the ischemic window to at least 24 hours. This increased time also permits procurement of distant livers, preventing waste of this scarce resource. The use of microvascular surgical techniques to aid in biliary reconstruction has decreased complications in biliary drainage. Many intraoperative technologic advances have improved the safety of these procedures. One of the most important is the use of an extracorporeal shunt to improve venous return to the heart while the liver is being replaced. This venovenous bypass is now used routinely in most centers, with many physiologic benefits. Significant blood loss and coagulopathy continue to present challenges in the care of these patients. A rapid infusion system enabling fluid replacement at the rate of 1500 mL/min at a warm temperature has proved helpful in many situations. Timely monitoring of coagulation is possible with the use of the thromboelastograph (TEG). This device permits appropriate intervention long before standard coagulation test results would be available.

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Liver transplantation has increased understanding of the important physiologic and metabolic roles of the liver. The anesthetic and critical care of these patients presents one of the most significant challenges in medicine today. It is to be hoped that a more complete understanding of the complexities involved will continue the trend of improved survival of these very ill patients.

Preoperative Considerations

Indications for Transplantation. The usual candidate for liver transplantation is a person with irreversible chronic progressive liver disease; however, as the mortality from the procedure has decreased, the indications have broadened. Chronological age has become less of a contraindication, with many recipients older than 60 years of age having successful liver transplants. Children with inborn errors of metabolism represent a significant pool of transplant candidates. Contraindications include systemic infection, severe coexisting disease that would limit survival (e.g., cardiac or pulmonary disease), and patient noncompliance. The alcoholic patient with cirrhosis must demonstrate compliance and a minimum period of abstinence (usually 6 months to 1 year) to be considered as a candidate. Controversial candidates include patients with primary hepatic malignancies, hepatitis B virus carrier state, and human immunodeficiency virus carrier state.

Regardless of individual institutional guidelines for recipient selection, it has become clear that the timing of the transplant is very important. It is no longer reasonable to consider transplantation as a last resort. Patient survival is clearly enhanced by performing transplantation before deterioration to the point of requiring life-support systems[23] (Fig. 1).

Pathophysiology of Liver Disease. *Hepatic Dysfunction.* Candidates for liver transplantation have varying degrees of hepatic dysfunction. Patients with neoplasms can have near normal liver function, whereas patients at the other extreme, with postnecrotic cirrhosis, can have severe hepatocellular disease and multiple organ involvement. Patients with cholestatic disease fall somewhere in between. The liver

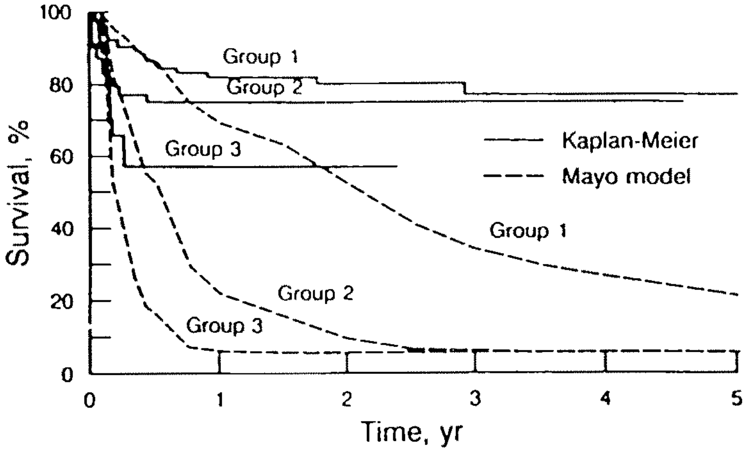

Figure 1. The influence of disease severity on the projected survival without transplant (Mayo model) versus the actual survival achieved with transplantation (Kaplan-Meier model). Group 1 patients were in the best condition and group 3 patients in the worst. (*From* Markus BH, Dickson ER, Grambsch PM, et al: Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 320:1709, 1989; with permission.)

has many important functions: (1) regulation of blood volume to maintain normovolemia; (2) excretion of bile, metals, and dyes; (3) metabolism of carbohydrates, fats, proteins, minerals, and vitamins; (4) detoxification; (5) hematopoiesis; and (6) destruction of red blood cells.[18]

Hypoglycemia can be seen in hepatic failure because of depletion of glycogen stores in the liver, decreased gluconeogenesis, and other hormonal interactions. High levels of circulating insulin are frequently seen, but insulin resistance is also known to occur in patients with liver disease.

Drug disposition in patients with liver disease is unpredictable. Depending on the type and severity of the hepatic dysfunction, different metabolic pathways can be affected to a greater or lesser extent. Liver disease also affects protein binding, volume of distribution, and absorption of drugs, and, therefore, careful titration of drugs is essential in these patients.

Cardiovascular System. Patients with cirrhosis and portal hypertension are usually in a hyperdynamic state with elevated cardiac output and low systemic vascular resistance. The low peripheral vascular resistance is due to increased levels of vasodilator substances either produced or not detoxified by the liver, such as glucagon, vasoactive intestinal polypeptide, prostaglandins, and others. Patients demonstrate arteriovenous shunting and decreased oxygen consumption, which results in increased mixed venous oxygen saturation. The sympathetic response to baroreceptor stimulation is impaired, and patients have a decreased sensitivity to catecholamines.[22] Ejection fraction may remain normal with a low systemic vascular resistance, even in the presence of impaired myocardial contractility, a frequent sequelae in the late stages of cirrhosis. Coronary artery disease is relatively uncommon in patients with liver disease, although myocardial infarction and unsuspected cardiomyopathy have been seen during liver transplantation. Ascites, with increased intra-abdominal and intrathoracic pressures, can embarrass cardiovascular performance by decreasing venous return and cardiac output.

Pulmonary System. Hypoxemia is common in patients with liver disease and portal hypertension because of intrapulmonary shunting, impairment of hypoxic pulmonary vasoconstriction, ventilation/perfusion abnormalities, alveolar hypoventilation, decreased pulmonary diffusing capacity, and a shift in the oxygen-hemoglobin dissociation curve (Fig. 2).

Renal System. Renal dysfunction is common with severe liver failure. One of the most common problems is sodium retention due to increased levels of aldosterone and decreased effective blood volume. Hyperaldosteronism is thought to be secondary to increased adrenal secretion as well as decreased degradation of the hormone. The decrease in effective blood volume occurs from redistribution of fluid to interstitial spaces and ascites and results in an increase in sympathetic nervous system activity and angiotensin concentrations, renin release, aldosterone secretion, and intrarenal blood flow redistribution.

Decreased water clearance is also common and is mainly due to enhanced antidiuretic hormone activity and decreased delivery of filtrate to the diluting segments of the nephron. Dehydration and gastrointestinal bleeding with consequent absorption of large amounts of nitrogenous substances from the gut contribute to renal dysfunction.

The hepatorenal syndrome may develop in patients with end-stage liver disease awaiting transplantation. The etiology is not completely understood, although it may be related to increased renin activity and aldosterone and norepinephrine concentrations in blood; prostaglandins (PGE_2) and kallikreins seem to provide a protective role. Treatment involves appropriate fluid loading, careful diuretic therapy, and small doses of dopamine (0.5–3 μg/kg/minute). Fortunately, the acute renal failure seen in hepatorenal syndrome is reversible. Kidneys transplanted from

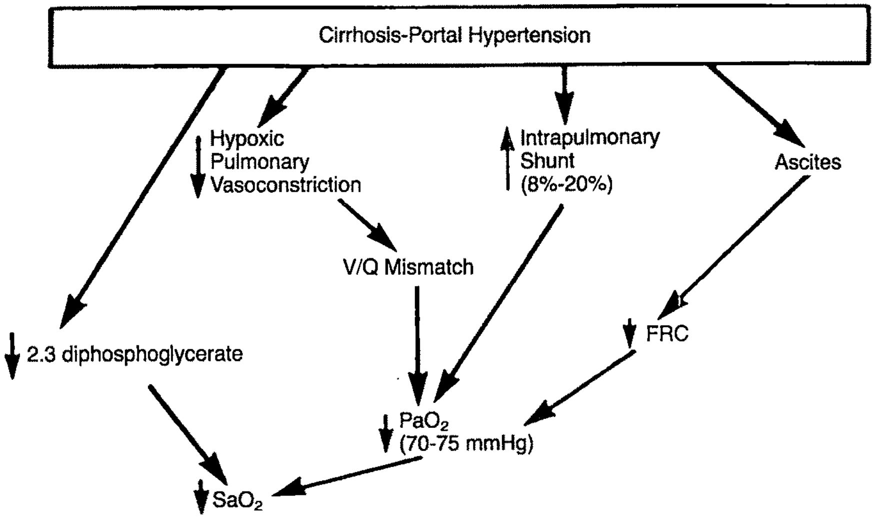
Cirrhosis-Portal Hypertension
↓ Hypoxic Pulmonary Vasoconstriction
↑ Intrapulmonary Shunt (8%-20%)
Ascites
V/Q Mismatch
↓ FRC
↓ 2.3 diphosphoglycerate
↓ PaO2 (70-75 mmHg)
↓ SaO2

Figure 2. Hypoxemia in liver cirrhosis and portal hypertension. (*From* Kang YG, Gelman S: Liver transplantation. *In* Gelman S (ed): Anesthesia and Organ Transplantation. Philadelphia, W.B. Saunders Company, 1987, p 146; with permission.)

patients with the hepatorenal syndrome can resume normal function in the recipient.[19]

Electrolytes and Acid-Base Balance. Blood volume is generally increased, but intravascular volume is often depleted secondary to ascites formation and diuretic therapy. Hyponatremia is common due to increased antidiuretic hormone activity and impaired water excretion. However, hypernatremia can also occur, particularly with improper fluid management. Hypokalemia is often seen, especially with diuretic therapy, vomiting and diarrhea, and inadequate potassium intake. Total body potassium is usually significantly depleted. However, in severe renal dysfunction, hyperkalemia can also occur, necessitating dialysis. Hypocalcemia, hyperphosphatemia, and hypomagnesemia are common.

Metabolic alkalosis often occurs secondary to hyperaldosteronism, vomiting, and diarrhea. Respiratory alkalosis with hyperventilation is also characteristic. However, severe metabolic acidosis is common in patients with acute fulminant hepatitis, rapidly progressing hepatic failure, or unrecognized infection.

Central Nervous System. Hepatic encephalopathy can occur in the advanced stages of liver failure. It is characterized by confusion, somnolence, asterixis, or deep coma. An increase in blood ammonia concentration is seen, although there is no specific correlation between the blood ammonia concentration and the severity of encephalopathy. Hepatic encephalopathy is thought to result from inadequate removal of certain substances by the liver, notably, nitrogenous compounds, mercaptans, short-chain fatty acids, false neurotransmitters, and gamma-aminobutyric acid. Several factors worsen encephalopathy: diuretic therapy, gastrointestinal hemorrhage, infection, and further hepatic damage. Management is supportive and can include aspiration of blood from the gastrointestinal tract, suppression of intestinal bacteria by oral administration of neomycin, administration of lactulose to facilitate ammonia excretion, dietary treatment, and correction of electrolyte disorders. In 50% of patients with acute fulminant hepatic failure brain edema develops.[15] When severe coagulopathy occurs, intracranial hemorrhage may develop.

Coagulation. Hepatic failure is invariably associated with coagulopathy, which has a multitude of causes. Thrombocytopenia occurs in 70% of patients due to bone marrow depression, hypersplenism, and disseminated intravascular coagulation. Impaired platelet function also may be present because many of the platelets produced are small and hypofunctional.[2] Coagulopathy is also caused by malabsorption of substrates, decreased production of liver-dependent clotting factors, and inadequate clearance of activated coagulation factors. All coagulation factors decrease except fibrinogen and Factor VIII. The prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged, and the inability to correct PT by vitamin K administration reflects severe liver dysfunction. Increased fibrinolytic activity results from decreased production of antiplasmin and inadequate clearance of tissue plasminogen activators. Fibrin degradation product levels become positive in one third of patients, suggesting the presence of a chronic disseminated intravascular coagulation. The preoperative degree of coagulopathy correlates significantly with the intraoperative blood product requirements.[24]

Anesthetic Management

Aggressive monitoring and intervention are essential for the successful outcome of liver transplantation. The goal of therapy is control of physiologic variables in an effort to maintain homeostasis. Obviously, rapid assessment of blood-gas tensions, acid-base balance, electrolytes, and coagulation status is imperative because these variables change so quickly during the procedure.

Patients should undergo thorough evaluation and counseling before arrival in the operating room. Preoperative medications for sedation are rarely necessary but, if needed, are best titrated carefully and administered intravenously under the supervision of the anesthesiologist. Typical monitoring parameters include an electrocardiogram, heart rate (stethoscope), arterial pressure, central venous pressure, pulmonary arterial pressure, and cardiac output. On-line monitoring of mixed venous oxygen saturation is often helpful in assessing cardiac performance. Pulse oximetry provides a constant measure of arterial oxygen saturation and serves to confirm serial measurements of arterial blood-gas tensions. A urinary catheter is inserted, and body temperature is monitored by measuring rectal, esophageal, and blood temperatures. Frequently, two arterial pressure monitoring catheters are used: one for constant pressure monitoring and the other for blood sampling and back-up pressure monitoring. Because of the intrinsic coagulopathy in these patients, heparin is usually omitted from the flush solutions used to keep the catheters patent. Because of the potential for tremendous blood loss, two large introducer sheaths (8.5 to 9 F) are typically placed—one in the antecubital vein contralateral to the axillary vein to be used for venovenous bypass and the other in the external or internal jugular vein. These catheters are connected to the rapid infusion device, permitting rapid infusion of warmed blood products. In pediatric patients, venous access depends on the size of the patient. Laboratory determinations performed during surgery include arterial and venous blood-gas tensions, assays for hemoglobin, hematocrit, sodium, potassium, ionized calcium, glucose, and lactic acid levels, and osmolality. Often, these are measured hourly or more frequently if needed. Coagulation is evaluated by use of TEG, PT, PTT, and platelet count. Determination of thrombin time, factor levels, fibrin split products, and euglobulin lysis time also can be helpful. TEG has the advantage of assessing the entire coagulation process, including coagulation and fibrinolysis, is readily available, provides useful information within 30 minutes, and permits careful titration of blood products and pharmacologic therapy for the particular coagulation defect present[20] (Table 1).

Generally, these patients should be considered to have full stomachs because of ascites, delayed gastric emptying, and occasional nausea and vomiting from cyclosporine A therapy. A rapid sequence induction is performed with preoxygenation, and the induction agent is chosen according to the preference of the

Table 1. *Coagulation Therapy Guided by Thromboelastographic Monitoring*

- Maintenance fluid
- RBC:FFP:Plasmalyte A = 300:200:250 ML
- Replacement therapy
  - FFP (2 U) for prolonged reaction time ($r > 15$ minutes)
  - Platelets (10 U) for small MA ($MA < 40$ mm)
  - Cryoprecipitate (6–12 U) for persistent slow clot formation rate ($a < 40^\circ$) with normal MA
- Pharmacologic therapy
  - Compare coagulability of whole blood, blood treated with protamine sulfate, and blood treated with epsilon aminocaporic acid
  - Epsilon aminocaporic acid (1 g) for severe fibrinolysis ($F < 60$ minutes)
  - Protamine sulfate (50 mg) for severe heparin effect
  - Heparin (1000–2000 U) for hypercoagulable state

From Kang YG: Anesthesia for liver transplantation. Anesthesiol Clin North Am 7:551, 1989; with permission.

Abbreviations: RBC = red blood cells; FFP = fresh frozen plasma; MA = maximum amplitude.

anesthesiologist and the cardiovascular stability of the patient. Commonly, thiopental, ketamine, fentanyl, or etomidate are used with succinylcholine administered to facilitate intubation. Although all potent inhalation anesthetics have been used to maintain anesthesia, isoflurane is chosen most frequently. Usually, fentanyl or other narcotic and neuromuscular blocking agents are used to supplement anesthesia. Nitrous oxide is generally avoided because of concern for air emboli, bone marrow depression, cardiovascular depression, and distention of bowel loops, making abdominal closure difficult. Maintaining desired levels of drugs at receptor sites is frequently difficult with massive blood transfusion and hemodynamic instability; however, anesthetic requirements seem to be reduced in patients undergoing liver transplantation, perhaps related to false neurotransmitters such as those implicated in the etiology of hepatic encephalopathy.

Surgical Technique

The operative procedure is divided into three distinct stages, each with its own unique problems. The first stage is termed the preanhepatic phase, during which careful surgical dissection of the diseased liver is performed. During this phase, significant surgical bleeding is often encountered because of the numerous collateral channels and previous surgical procedures. Surgical manipulation with compression of the inferior vena cava, portal vein, and hepatic artery can compromise venous return and cardiac output.

The anhepatic stage begins with the hepatectomy and ends when the vascular anastomosis of the inferior vena cava and portal vein is complete. Simple cross-clamping of the inferior vena cava and portal vein can decrease venous return to 50% of normal and cause hemodynamic compromise. This frequently necessitates administration of fluid and vasopressors. The technique of venovenous bypass was developed to minimize physiologic derangements during hepatectomy and is now the most commonly used.[32] Cannulas are inserted into the femoral and portal veins, and the blood is diverted to the axillary vein via a centrifugal bypass system. The apparatus does not necessitate systemic heparinization and has a flow rate as much as 40% of cardiac output. With this technique, hemodynamic instability is minimized, surgical bleeding is lessened, and visceral and renal venous congestion are relieved.

Before completion of the infrahepatic vena caval anastomosis, the donor liver is flushed with lactated Ringer's solution via the portal vein to remove potassium, preservation solution, air, and metabolites. The portal venous anastomosis is then completed, and the neohepatic phase begins with reperfusion of the graft liver by unclamping the suprahepatic, infrahepatic vena cava, and portal veins. The reperfusion of the liver is followed by hepatic arterial anastomosis, hemostasis, and biliary reconstruction. Finally, an intraoperative cholangiogram is obtained to determine patency of the biliary drainage system.

Intraoperative Problems

The primary intraoperative difficulties that occur include hypotension, blood loss, electrolyte imbalance, arrhythmias, and coagulopathy. It can be useful to consider the major organ systems in relation to the three phases of liver transplantation.

Cardiovascular System. During the preanhepatic stage, cardiovascular instability often occurs due to surgical bleeding, vascular compression, and drainage of ascites. The degree of blood loss depends on the amount of hilar scarring, portal hypertension, and coagulopathy. Hypotension is treated with volume replacement and calcium chloride to maintain a normal ionized calcium level. Occasionally, a vasopressor may be needed, and dopamine (3–10 μg/kg/min) is usually the preferred agent.

During the anhepatic phase, venous return can be severely compromised, and venovenous bypass is often used in patients weighing more than 20 kg to ameliorate the physiologic derangements. Decompression of the portal and caval systems is also thought to decrease blood loss and improve renal perfusion and function. This centrifugal bypass system is dependent on the blood volume to maintain adequate flow. Because the system does not utilize heparin, it is important that the flow be kept at a level high enough to avoid thromboembolism in the circuit. It is customary to discontinue bypass if the flow is less than 1 L/min because the bypass system seems to activate coagulation when flow is less than 800 mL/min.[11]

At the initiation of bypass, thrombus or air can be embolized from the bypass circuit to the pulmonary or cerebral circulation. Particular attention to this problem at the initiation of bypass is necessary, although emboli can occur at any time. Once bypass is well established, the patient is usually hemodynamically stable during the second stage. At the end of the second stage, it is imperative that acid-base and electrolyte abnormalities be corrected and that the new liver be flushed out adequately to minimize the hemodynamic changes associated with reperfusion of the liver.

With the start of the reperfusion phase, hemodynamic instability is the rule rather than the exception. Problems include hypotension, bradycardia, arrhythmias, and, occasionally, cardiac arrest. Cardiac output, mixed venous oxygen tension, and systemic vascular resistance are decreased, and pulmonary arterial and central venous pressures are substantially increased. This constellation of events is often called the "postreperfusion syndrome" and can be severe, necessitating full-scale resuscitation.[1] The etiology may be related to the wash-in of cold hyperkalemic acidotic preservation solution from the newly perfused liver. However, symptoms often persist when the temperature and potassium have normalized, suggesting causation by vasoactive substances released from the grafted liver. Treatment typically involves administration of calcium chloride, sodium bicarbonate, and small doses of epinephrine (5–10 μg). Usually, glucose and insulin therapy to combat hyperkalemia is not needed because it is typically transient. One must be careful not to overload the patient with fluid at this time because filling pressures are usually already increased. Overzealous fluid administration can result in additional cardiac workload, increased impedance to hepatic blood outflow, and subsequent impairment in hepatic blood flow and oxygen supply.

After the patient has stabilized, the hepatic arterial anastomosis is performed.

With retroperitoneal dissection, blood loss can be significant and must be treated appropriately.

Pulmonary System. Mechanical ventilation with moderate levels of positive end-expiratory pressure usually serves to expand atelectatic portions of the lung. Usually, adequate blood gases can be maintained with oxygen concentrations of 40% to 70%. If a significant pleural effusion is present, thoracentesis, performed at the beginning of surgery, may prove helpful.

Occasionally, pulmonary edema develops intraoperatively related to heart failure or fluid overload. Unfortunately, this condition usually does not respond well to diuretic therapy and is often fatal.

Blood Coagulation. Fluid administration is guided by hemodynamic measurements and urine output. A constant fluid mixture consisting of one unit of packed red blood cells, one unit of fresh frozen plasma, and 250 mL of Plasmolyte A is administered via the rapid infusion system. This mixture will maintain a hematocrit of approximately 27% and delivers adequate factor levels to promote hemostasis. The volume of blood transfused varies, ranging from less than 10 units to greater than 200 units of packed red blood cells; however, blood usage has decreased as individual programs have developed more experience. Major surgical bleeding still occurs even in the most experienced hands, and the anesthesiologist and blood bank personnel must be prepared to administer massive quantities of blood.

Thromboelastography is used to monitor the coagulability of whole blood. During the preanhepatic stage, a dilutional coagulopathy may develop superimposed on the patient's intrinsic coagulopathy. This situation must be treated aggressively from the beginning of surgery. During the anhepatic stage, platelets and cryoprecipitate are withheld to avoid thromboembolic complications of bypass. Marked fibrinolysis can occur during the anhepatic stage, but treatment is usually delayed until 30 minutes following reperfusion. Therapy is then guided by TEG parameters. Pharmacologic therapy can include administration of epsilon aminocaporic acid if severe fibrinolytic activity is present and the drug's effectiveness is confirmed by in vitro testing. Severe coagulopathy should improve gradually during the neohepatic stage unless the grafted liver functions poorly or major surgical bleeding occurs. In those situations continuous replacement therapy is required.

Renal System. Oliguria is not uncommon intraoperatively but has been less problematic since the introduction of venovenous bypass. A low dose of dopamine (2–3 μg/kg/min) is often used for renal protection, although its efficacy is controversial. Polson and coworkers[30] reported better postoperative renal function in patients who received prophylactic low-dose dopamine (2 μg/kg/minute) following mannitol (1 g/kg) than in those who received only mannitol. Driscoll and colleagues[12] have suggested that low doses of furosemide can provide a protective effect against cyclosporine-A–induced renal injury in liver transplantation.

Fluids and Electrolytes. The initial hyponatremia and hypokalemia often seen in liver transplantation will correct itself over time with administration of blood products and a balanced electrolyte solution. If renal function is inadequate, hyperkalemia can become problematic due to the large volumes of banked blood administered. This may necessitate washing the red blood cells and administration of intravenous calcium chloride and sodium bicarbonate. During the neohepatic stage, potassium levels decrease gradually due to uptake by the new liver. Occasionally, judicious potassium supplementation may be needed. Hypernatremia often occurs due to the repeated administration of sodium bicarbonate to treat metabolic acidosis.

Ionized calcium levels must be monitored carefully and treated aggressively. Levels decrease progressively during the preanhepatic and anhepatic stages due to rapid transfusion and citrate intoxication. If left untreated, cardiovascular impairment will occur.

Progressive metabolic acidosis is common[7] and is caused by rapid transfusion of acidotic blood, decreased metabolism of citrate, lactate, and other acids by the diseased or absent liver, and decreased tissue perfusion (Fig. 3). Base deficit is generally corrected with frequent doses of sodium bicarbonate to minimize the cardiovascular instability during graft reperfusion. After reperfusion, base deficit gradually decreases in most patients, and metabolic alkalosis may actually occur in some patients by the end of surgery.

Theoretically, hypoglycemia is of concern in patients with liver failure who are undergoing transplantation. However, it is rare, and glucose levels generally remain normal, probably due to a decrease in glucose utilization and the administration of glucose contained in transfused blood. Hyperglycemia is often seen following reperfusion, probably due to release of glucose from the donor liver. Glucose levels can remain high for several hours.

Temperature. Body temperature gradually falls when operation is begun, especially if massive transfusion is required. A further drop occurs when the venovenous bypass is begun, because it does not incorporate a heat exchanger. Body temperature typically falls 1 to 2° C on reperfusion of the graft liver and then gradually returns to 34 to 35° C by the end of operation. Measures to combat hypothermia include warming of blood products, use of a heating blanket, use of a humidifier in the breathing circuit, irrigating the abdominal cavity with warm solution, and raising the ambient operating room temperature.

Postoperative Intensive Care

Intensive care of these patients requires continued attention to many of the same problems encountered intraoperatively. These include cardiovascular instability, coagulation status, renal function, pulmonary insufficiency, and electrolyte imbalance. In addition, immunosuppression and its sequelae, infection control, and pain management must be considered.

Most patients show remarkable cardiovascular stability in the intensive care unit. As their temperature normalizes, vasodilation occurs and necessitates increased fluid intake. Postoperative hypertension is quite common and responds well to sodium nitroprusside, nitroglycerin, hydralazine, diuretics, and beta-blocking agents.

Pulmonary care is critical in these patients. Most patients are extubated within

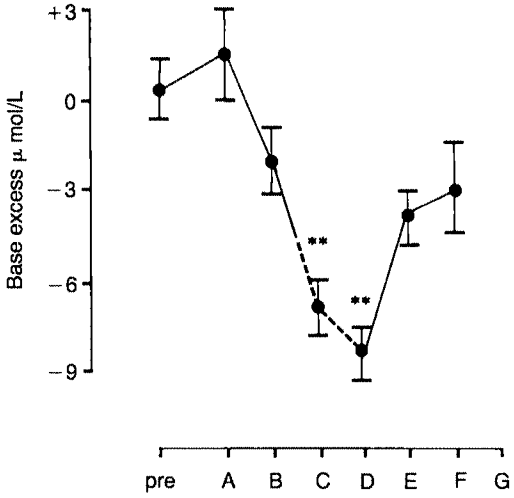

Figure 3. Changes in base deficit during liver transplantation. Mean SEM of nine patients. A = after induction of anesthesia; B = dissection of the liver; C = beginning of the anhepatic stage; D = reperfusion of the graft liver; E = biliary reconstruction; F = skin closure; and G = end of surgery. $P < 0.01$ versus preoperative values. (*From* Carmichael FJ, Lindop MJ, Farman JV: Anesthesia for hepatic transplantation: Cardiovascular and metabolic alterations and their management. Anesth Analg 64:108, 1985; with permission.)

48 hours of operation. Atelectasis and pulmonary effusion are common. Adult respiratory distress syndrome can occur and is frequently associated with sepsis or rejection.

Central nervous system complications can occur. Mental confusion usually improves as the liver begins to function well. Seizures are common and may be associated with cyclosporine A therapy. Intracranial hemorrhage can occur, especially in thrombocytopenic patients with hypertension.

Renal dysfunction can occur, although persistent renal failure is uncommon. The development of renal failure is associated with a high mortality.

Metabolic alkalosis is frequently observed postoperatively but should not cause undue concern. It occurs secondary to metabolism of citrate and lactate, steroid therapy, drainage of gastric contents, potassium depletion, and diuretic therapy. A recent study demonstrated that postoperative metabolic alkalosis did not relate to the volume of blood given intraoperatively or to the dose of sodium bicarbonate.[14] Furthermore, 70% of patients with postoperative metabolic alkalosis survived, whereas all patients with metabolic acidosis died. Persistent metabolic acidosis is a sign of poor hepatic function. Total serum calcium is often elevated, but the ionized fraction can remain normal or depressed.

The graft liver may begin to function within a few hours of admission of the patient to the intensive care unit. The levels of citrate, lactate, and glucose should gradually decrease, and coagulation parameters will normalize. Bile production should also occur. Liver enzyme levels can be high because of preservation injury, but they gradually return toward normal in the postoperative period.

The most common hepatic complication is rejection of the graft liver. One may also see primary nonfunction of the graft, thought to be related to prolonged ischemia of the donor organ. Retransplantation is frequently performed in these instances and has contributed to improved survival. Unfortunately, clinically significant extrahepatic complications occur frequently in these patients (Table 2).

A recent study showed the main causes of death in the Intensive Care Unit to be infection (55%) and hemorrhage (19.8%).[27] Multisystem failure and renal failure comprised 60% of all contributory causes of death.

Obviously, rational care of these critically ill patients mandates a coordinated effort among multiple disciplines. We have seen a tremendous improvement in care and survival of these patients over the last decade. It is hoped that this trend will continue as an improved understanding of the pathophysiology of the disease process develops.

CARDIAC TRANSPLANTATION

Cardiac transplantation is being performed with increasing frequency worldwide. The first human heart transplant performed in 1967 generated tremendous excitement, and many programs attempted the procedure in 1968 and 1969.[3] However, the results were so dismal and the 1-year mortality rate so high that cardiac transplantation was almost completely abandoned throughout the 1970s. In the late 1970s, cyclosporine A, a potent immunosuppressant, was introduced, which improved survival rates by improving the balance between immunosuppression and infection. Since 1980, increasing numbers of heart transplants have been performed in more centers around the world. Only five centers were performing heart transplants in 1978; in 1988, 173 centers were performing heart transplants, with 118 of these centers in the United States. From 1980 to 1989, more than 9000 persons underwent cardiac transplantation. The 1-year survival has increased from 22% in 1968 to more than 80% in 1991. The 5-year survival is currently around 70%.[4] More importantly, more than 90% of these critically ill patients achieve New

Table 2. *Clinically Significant Postoperative Extrahepatic Complications in 225 Hepatic Transplant Recipients*

COMPLICATION	NO. OF PATIENTS
Cardiovascular system	
Arrhythmia	6
Acute myocardial infarction	3
Endocarditis	3
Pulmonary system	
Infection	42
Pleural effusion necessitating thoracentesis	40
Atelectasis necessitating bronchoscopy	42
Respiratory failure necessitating tracheostomy	25
Aspiration pneumonia	7
Persistent pneumothorax	3
Renal system	
Renal failure	70
Central nervous system	
Seizure	23
Intracranial hemorrhage	10
Meningitis	3
Psychosis and depression	5
Digestive system	
Hemorrhage	21
Perforation of the bowels	9
Obstruction	8
Pancreatitis	5
Hematologic system	
Lymphoma	5
Hodgkin's disease	1
Surgical complications	
Surgical bleeding	5
Medical bleeding	14
Biliary tract complications	40
Intra-abdominal infection	57
Wound complications	25
Other	
Thrombophlebitis	6
Decubitus ulcer	7
Multiple vertebral fracture	4
Infected seroma	7
Tooth abscess	3
Brachial plexus injury	2
Knotty pulmonary artery catheter	1

Reprinted from Kang YG, Gelman S: Liver transplantation. *In* Gelman S (ed): Anesthesia and Organ Transplantation. Philadelphia, W.B. Saunders, 1987, p 177; with permission. (Data for table based on Wood RP, Shaw BW Jr, Starzl TE: Extrahepatic complications of liver transplantation. Semin Liver Dis 5:348, 1985)

York Heart Association Class I functional status postoperatively and resume productive lives in their communities. Thus, health care professionals have increasing opportunities to care for heart transplant patients outside the transplant center environment. In approximately 15% to 30% of these patients, conditions necessitating surgical therapy develop postoperatively, often emergently.[26] Therefore, an appreciation of the surgical procedure, complications, and differences in patients having cardiac transplantation is essential in optimizing care.

Preoperative Considerations

Patients undergoing cardiac transplantation have end-stage heart disease, usually with decompensating heart failure. In the vast majority of patients, the etiology of the heart disease is either idiopathic cardiomyopathy or ischemic cardiomyopathy. The patient usually presents for operation while taking multiple medications to control the congestive heart failure and arrhythmias. As the cardiac function deteriorates, oxygen transport to tissues becomes impaired and associated organ dysfunction is common, especially renal, pulmonary, and hepatic compromise. Ream and colleagues[31] observed that the cardiovascular state typical of these patients would ordinarily be a contraindication for a surgical procedure but, instead, becomes the indication for operative intervention.

An understanding of the pathophysiologic features of dilated cardiomyopathy is essential for the safe conduct of anesthesia in these patients. The cardiomyopathies are characterized by abnormal contractility, preload dependence, and afterload sensitivity.[8] Impaired contractility is associated with beta-1-receptor downregulation, thought to be produced by chronic exposure of the heart to excessive catecholamine levels. These patients chronically maintain a state of maximal sympathetic outflow to support failing circulation. Receptor downregulation is associated with both a decrease in affinity of the receptor to agonist and an actual loss in numbers of beta-1 receptors. The practical result of these changes is that many of the inotropic drugs used show markedly diminished effectiveness. This problem is especially prominent in patients who come to the operating room in a decompensated state and already receiving vasoactive infusions. Much higher doses may be required intraoperatively, or alternative inotropes, which bypass the beta-1 receptor, may be necessary.

The Frank-Starling curve is often used to express the close relationship of ventricular stroke volume to end-diastolic volume. In the normal heart, a small increment in end-diastolic volume (preload) produces a large increase in stroke volume (Fig. 4). In the failing heart, the curve is displaced downward and flattened; volume loading in these patients does not produce the expected increase in stroke volume and can in fact cause a decrease in cardiac output. However, it must be kept in mind that any decrease in preload can cause rapid decompensation and circulatory collapse. In that regard, these patients have been termed "preload-dependent," i.e., the preload must be kept relatively high to keep these patients in a chronic state of marginal compensation.

The third aspect of importance in these patients is the concept of afterload sensitivity. Ventricular afterload consists of the wall stress sustained by the ventricle during systole. The two principal determinants of afterload are ventricular geometry and the instantaneous systolic backpressure within the ventricle created when the ejected stroke volume encounters the impedance of the arterial circulation.[10] Because of its geometric changes, the dilated heart has lost its ability to unload itself early in systole. Peak systolic pressure generated by the failing heart is decreased because of the increase in wall stress, present due to ventricular dilation.[28] Therefore, anything that increases systemic vascular resistance causes a significant decrement in stroke volume, cardiac output, and systemic perfusion. It must also be remembered that these patients often have such poor contractility that they are unable to generate a hypertensive response to surgical stimulation.[36] Instead of the typical inotropic response from activation of the sympathetic nervous system, these patients manifest decreased stroke volume, increased left ventricular end-diastolic volume, and the potential to progress to circulatory collapse.

With these factors in mind, the focus of the preoperative visit is slightly different than that for a routine elective procedure. Usually, it is difficult to optimize the patient's condition any further because of both intrinsic patient disease and time constraints. These patients have usually undergone a very thorough work-up by a cardiologist, transplant surgeon, and other specialists. It is helpful to review

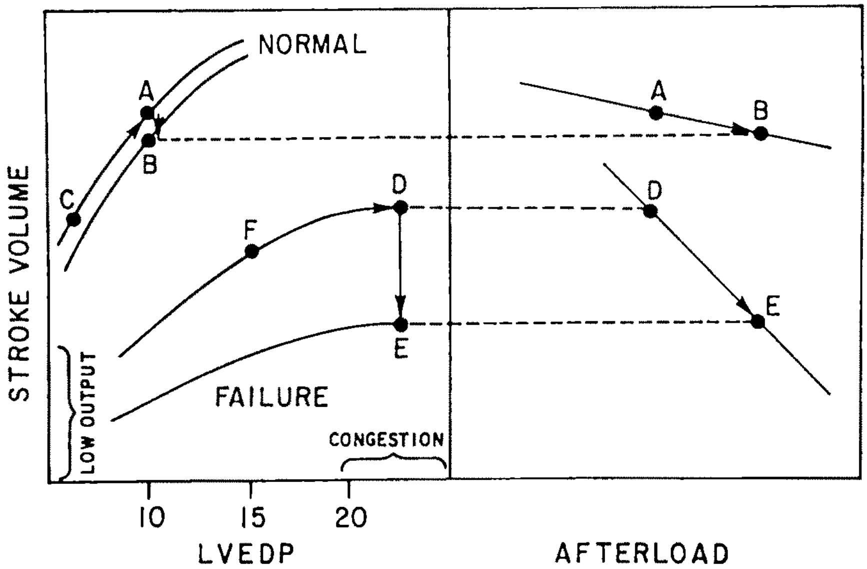

Figure 4. Frank-Starling curves *(left panel)* of a normal heart and a failing heart, and the impact of increased afterload on each heart's stroke volume *(right panel).* Whereas an increase in afterload of the normal heart produces only a small decrement in its stroke volume (*A* and *B*, either panel), an equivalent increase in the failing heart's afterload produces a much greater decrease in its stroke volume (*D* and *E*, either panel). (*From* Clark NJ, Martin RD: Anesthetic considerations for patients undergoing cardiac transplantation. J Cardiothorac Anesth 2:519, 1988; with permission.)

the catheterization data to assess the degree of ventricular dysfunction in an attempt to predict the patient's tolerance to anesthetics and to plan for resuscitative maneuvers. Pulmonary vascular resistance and its response to vasodilators is extremely important because right ventricular failure is the most common cause of the inability to wean the patient from cardiopulmonary bypass.[16] Current medications should be reviewed, and any recent changes in physical status should be assessed. These patients are considered to have full stomachs because of the emergent nature of the operation and because the vast majority receive oral cyclosporine A preoperatively. Sedative premedication is usually not considered necessary, but aspiration prophylaxis is often used.

The status of the cardiac donor must not be forgotten. Once brain death is established, the donor harvest is usually carried out expeditiously before further physiologic deterioration occurs. The anesthetic care of the donor can be challenging and deserves careful attention to optimize the status of the organs to be harvested. These patients have an inherently unstable cardiovascular system. Brain death causes a loss of vasomotor tone. Because of increased intracranial pressure, the donors have often received diuretics and may be hypovolemic and hypotensive. Diabetes insipidus is common and can result in hyperosmolarity and electrolyte imbalance. Donors are often hypoxemic secondary to neurogenic pulmonary edema and may also be prone to hypothermia. Careful attention must be paid to each of these problems. The goal should be to maintain optimal organ perfusion. Volume resuscitation, including blood products as needed, is almost always necessary, and the use of vasopressors should be minimized. It is also essential to coordinate the donor harvest carefully with the various surgical teams with good communication to the recipient operating room to minimize the ischemic time. Most programs prefer to limit the ischemic time to 4 hours or less, although the true upper limit for cardiac ischemic time is not known.[9]

Surgical Procedure

The technique for orthotopic cardiac transplantation has not changed appreciably since its description in the 1960s by Lower and Shumway.[21] The transplant patient's diseased heart is exposed by a midline sternotomy, and aortic and bicaval cannulation is performed following heparinization. After cardiopulmonary bypass is established, the aorta is cross-clamped and the heart is removed, leaving the posterior atrial walls with attachments of the pulmonary veins and vena cava intact. The donor heart is prepared by closing the patent foramen ovale, if present, and creating a large opening into the left atrium by connecting the orifices of the pulmonary veins. Residual tissue is trimmed to fit the cuff of the excised left atrium of the recipient, and then the left atria are connected with a running suture. An opening is made into the right atrium of the donor heart, and then the right atria are connected in a similar fashion. Next, the aortas are connected and then the pulmonary arteries. Air is evacuated, the cross-clamp is removed, and rewarming is completed. Usually the heart resumes a spontaneous rhythm but occasionally defibrillation is required. The patient is weaned from cardiopulmonary bypass in the usual fashion, and temporary pacing wires are attached to the right atrium and ventricle.

Anesthetic Management

Clark and Martin[8] summarized the challenge of anesthetizing patients undergoing cardiac transplantation: "the transplant anesthesiologist is often charged with caring for the marginally compensated patient who is already maximally using all available physiologic mechanisms for maintaining cardiac output at rest." Keeping that concept in mind, a few points deserve special emphasis.

Induction of anesthesia represents a particularly critical time for these patients. The risk of aspiration must be considered. Some clinicians advocate a rapid sequence induction, often with ketamine or etomidate and succinylcholine. These drugs can be supplemented with a benzodiazepine or a narcotic or both. Other practitioners prefer a more gradual technique with slow administration of narcotics and a nondepolarizing muscle relaxant, maintaining cricoid pressure throughout. Many different anesthetic agents have been used successfully for cardiac transplantation. It probably does not matter greatly which anesthetic agents are chosen as long as attention to the pathophysiology of the patient and to drug interactions are maintained. Because the patient's cardiac output is impaired, the patient typically shows a delayed but dramatic response to induction agents. Ablation of sympathetic outflow and positive pressure ventilation, in combination with the myocardial depressant effects of the anesthetic agents, can cause circulatory collapse. The physician must be prepared to provide inotropic support to these patients as needed.

Sterile technique is crucial; infection remains the leading cause of death in this patient population. Intraoperative monitoring is similar to that used during other major cardiac operations. Most centers routinely use a blood pressure cuff, multilead electrocardiogram, esophageal stethoscope, pulse oximeter, urinary catheter, radial arterial catheter for direct measurement of arterial blood pressure, temperature probe, and central venous catheter. The question of pulmonary artery versus central venous monitoring is somewhat controversial. A recent survey of 34 transplant centers reported that 32% were using pulmonary artery catheters prebypass and that 44% were using pulmonary artery catheters postbypass.[16] Of those using central venous catheters, 50% thought a pulmonary artery catheter would have been helpful in postbypass management. A pulmonary artery catheter can be extremely useful in those patients with high pulmonary vascular resistance. In this setting, the ideal monitor may actually be the thermal dilution right ventricular ejection fraction catheter.[17] This catheter permits determination of cardiac output, right ventricular end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction. If a pulmonary artery catheter is used, a sterility sheath permits the pulmonary artery catheter to be withdrawn during the cardiectomy and repositioned in the pulmonary artery after cardiopulmonary bypass.

Following cross-clamp removal, an isoproterenol infusion is frequently begun and titrated to increase the heart rate to approximately 100 to 120 beats per minute. The newly transplanted heart is usually bradycardic, often with a junctional rhythm. Isoproterenol is useful as both a chronotrope and an inotrope; it also enhances diastolic relaxation and improves ventricular filling. The new allograft often shows diminished contractility from prolonged ischemia. Therefore, optimization of volume status and heart rate is critical in maintaining adequate cardiac output. Additional inotropic support may also be necessary, especially if right ventricular failure is a problem.

Right ventricular failure is the most common cause of the inability to wean the patient from cardiopulmonary bypass (Fig. 5). Preexisting pulmonary hypertension predisposes the patient to this condition, and patients are usually rejected for transplantation if their pulmonary vascular resistance is greater than 6 Wood units. However, even with mild preexisting disease, severe acute pulmonary hypertension of unknown etiology can be seen after bypass. Hemodynamically the patient will have elevations of pulmonary artery, right ventricular, and central venous pressures along with decreased left atrial or pulmonary artery wedge pressures. A significant gradient between pulmonary artery diastolic and pulmonary artery wedge pressures develops. The lungs can appear pale, and the right ventricle can become grossly distended. Blood is unable to traverse the pulmonary bed adequately to load the left heart, and systemic hypotension develops. Successful outcome depends on effective pulmonary vasodilation; many agents, including isoproterenol, nitroglycerin, sodium nitroprusside, amrinone, and prostaglandin E_1, have been used. Hyperventilation and correction of metabolic acidosis can also relieve the vasoconstriction. Occasionally, institution of mechanical right ventricular support can be effective.[13]

Unique to the posttransplant setting is the fact that the allograft is totally dated. The heart retains the normal response to volume loading via the

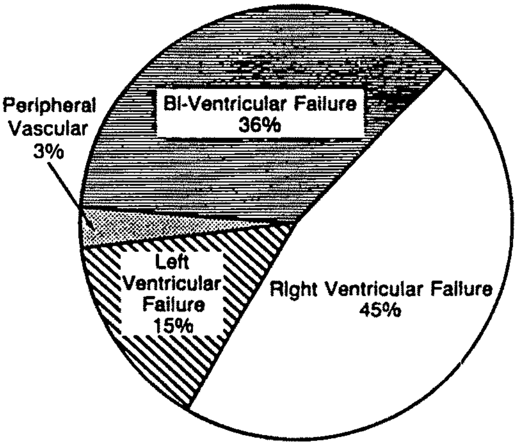

Figure 5. Causes of the inability to terminate cardiopulmonary bypass in the 33 survey patients who died in the operating room. (*From* Hensley FA Jr, Martin DE, Larach DR, et al: Anesthetic management for cardiac transplantation in North America, 1986 survey. J Cardiothorac Anesth 1:429, 1987; with permission.)

Frank-Starling mechanism. Normal electrical impulse formation and conduction are preserved, and coronary autoregulation remains intact with the appropriate increase in coronary flow in response to increased metabolic demand. Resting coronary blood flow is increased secondary to a lack of basal alpha-adrenergic tone.

Because the heart is denervated, any physiologic responses necessitating autonomic innervation are lost. Thus, the baroreceptor reflex can no longer occur, and responses to acute changes need time for alterations in circulating catecholamines. Patients demonstrate a delayed response to any stress, including exercise, venodilation, or hypovolemia.

Patients undergoing cardiac transplantation have an altered response to many drugs. Any medications that exert their actions via the autonomic nervous system will not elicit the expected response. The denervated heart shows its most consistent and reliable responses to agents that activate receptors directly. Agents with mixed actions can produce unpredictable responses; thus, isoproterenol, dobutamine, and epinephrine (direct-acting agents) have similar actions in the denervated heart. Norepinephrine produces its usual inotropic and vasoconstrictive response; however, the reflex slowing of the heart often seen with the rise in blood pressure no longer occurs. Dopamine, ephedrine, metaraminol, and mephentermine are partially indirect-acting drugs, and their actions may be somewhat diminished, although dopamine and ephedrine have been found to be useful clinically.[8] Calcium and glucagon continue to exert their usual positive inotropic effect. Drugs that affect heart rate through vagal influences are ineffective; therefore, atropine, anticholinesterases, and pancuronium do not change heart rate. Verapamil has been shown to decrease heart rate and atrioventricular nodal conduction. Nifedipine does not change heart rate or atrioventricular conduction. Digoxin continues to produce an inotropic effect but does not change atrioventricular nodal conduction acutely. With chronic use, however, digoxin produces a decrease in atrioventricular nodal conduction. Other antiarrhythmic agents have not been studied as extensively. Lidocaine and phenytoin exert their actions almost entirely independently of the autonomic nervous system and remain useful in heart transplant patients. Quinidine and procainamide have both direct and indirect actions. The direct effect includes suppression of the sinoatrial (SA) and atrioventricular nodes and His-Purkinje conduction. The action of bretylium is not well understood but may depend significantly on the autonomic nervous system. Insufficient experience exists to recommend its use in heart transplant patients. Beta-blockers have been used and are effective in decreasing heart rate and atrioventricular conduction velocity; however, caution must be exercised in their use because the negative inotropic properties can be quite evident in these patients.

Postoperative Management

Other than an appreciation for the previously mentioned differences in the denervated heart, the approach to postoperative management of patients undergoing cardiac transplantation is similar to that of other patients undergoing cardiac operation. Extubation is usually accomplished within 12 to 18 hours after operation. The isoproterenol infusion is usually continued for a few days because premature discontinuation can be associated with the sudden development of bradycardia and hypotension.

Infection remains the leading cause of death in these patients, and aseptic technique is mandatory. An attempt is made to remove invasive catheters as soon as possible to minimize the risks to the patient. Because the pulmonary system is the most common source of infection, a particularly aggressive approach must be taken when interstitial infiltrates occur. Bronchoscopy with lavage and transbronchial biopsy can be helpful, although one should not hesitate to perform an early open-lung biopsy for diagnosis. In addition to infection with common bacterial pathogens, these patients are also prone to infection with opportunistic pathogens (such as cytomegalovirus, *Pneumocystis carinii, Legionella pneumophilia,* fungi, and others).

Various immunosuppressive agents and regimens have been used in these patients, including cyclosporine A, corticosteroids, azathioprine, cytoxan, OKT3, and antilymphocyte sera. A detailed review of these agents can be found elsewhere[5] and is beyond the scope of this discussion. Cyclosporine administration is almost universally associated with the development of hypertension requiring long-term therapy. The goal of immunosuppression therapy is to combat rejection effectively with the lowest possible dose of medication and, thereby, avoid unwanted side effects. Routine endomyocardial biopsies have been very helpful in monitoring rejection episodes and permitting effective treatment. More recently, effective diagnosis and management of rejection episodes has been accomplished with noninvasive echocardiographic and clinical criteria.[6] Further developments in noninvasive monitoring of immunosuppression are crucial, particularly as more infants and children are undergoing transplantation.

Postoperative surgical complications often develop in these patients. In addition to mediastinal hemorrhage, in a surprising number of patients general surgical complications develop, including sigmoid and small bowel perforation, acute cholecystitis, pancreatitis, and gastrointestinal bleeding. The mortality rate in one series of such patients was 25%, illustrating the need for early and aggressive diagnosis with operative intervention.[35]

Unfortunately, cardiac transplantation is associated with significant long-term complications. Although more than 90% of the rejection episodes occur in the first year after operation, long-term causes of death include suicide, malignancy, and graft atherosclerosis. Severe graft coronary atherosclerosis develops in 30% to 40% of recipients within the first 3 years following transplantation. It is thought to be immunologically mediated and because of the denervation of the heart, is not associated with angina. It is a diffuse problem not amenable to coronary artery bypass grafting and, thus, mandates retransplantation. Graft atherosclerosis was the most common reason for retransplantation procedures performed at Stanford University in the first 14 years of their experience.[29] Thus, a high index of suspicion for significant coronary artery disease must exist for any patient requiring care 2 to 3 years after transplantation.

SUMMARY

Clearly, remarkable progress has been made in the last 20 years in improving the outlook for survival in these critically ill patients. It is to be hoped that during the next 20 years we will witness exciting breakthroughs in many areas, including immunomodulation, pharmacology, and infection control.

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Treatment of the Drug-Overdosed Patient in the Intensive Care Unit

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EPIDEMIOLOGY

The number of persons who use drugs can only be estimated roughly. Data are usually obtained from participating emergency rooms, drug rehabilitation centers, and surveys of households and schools. Homeless persons, prisoners, and individuals without a mailbox or telephone are often excluded. Information obtained is also dependent on the honesty of the person sampled.[41] Available data are therefore imperfect and do not accurately reflect the true population usage.

Unintentional poisoning is defined as the ingestion, inhalation, injection, or absorption of a chemical agent that results in injury or death. It is one of the top 10 causes of accidental morbidity and mortality in the United States.[59] More than 2.1 million cases of human poisoning were reported to all United States Poison Control Centers in 1989. This is an 8.7% increase from that reported in 1988. Of all reported cases, 9.7% were secondary to intentional substance exposures. Drug abuse, which can be defined as the improper use of a substance for a psychotropic effect, accounted for 1% of the intentional substance exposures. A total of 590 fatalities were reported to poison control centers in 1989. Of these, 64 or 11% were secondary to drug abuse.[55] Results from the Household Survey of the National Institute on Drug Abuse (NIDA) revealed that almost 28 million Americans used illicit drugs in 1988 and more than 21 million Americans used cocaine at least once. Although abuse of certain drugs has declined, e.g., marijuana,[65] use of other substances, such as cocaine, has been on the rise. The NIDA Household Survey illustrates that excluding ethanol, cocaine was the most frequently used drug by all groups in 1988. This was followed by narcotic analgesics, stimulants, tranquilizers, sedatives, hallucinogens, and inhalants. The highest usage was reported in the 18 to 25-year-old age group, with males having a higher frequency of drug use than females. Tranquilizers are a notable exception to this trend because their use is higher among females and older age groups. Stimulants and sedatives also are used more frequently in older age groups.[65]

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Intentional and accidental drug overdoses are a major medical problem. Ten percent of all ambulance calls are for suspected overdose. Fifteen to twenty percent of all medical admissions and fifteen percent of all admissions to the intensive care unit (ICU) are for poisoning and drug overdose.[36, 58] With appropriate therapy, the in-hospital mortality rate from drug overdose is less than 1%.[55, 58] Fatalities frequently occur before the patient reaches a medical facility and are usually due to anoxic brain damage. The Drug Abuse Warning Network (DAWN), a monitoring network of emergency departments and medical examiner offices through the NIDA, reported 7,162 deaths directly or indirectly associated with drug use. Cocaine and narcotic-analgesics were mentioned in almost 50% of these fatalities. Mortality rates for drug users were two times higher for males than for females and higher in blacks of both sexes than for whites. Deaths associated with tranquilizer, sedative, and amphetamine use were at least three times higher for whites than for blacks.[64]

RECOGNITION

Without a reliable history, the diagnosis of drug overdose can be difficult. Only a few groups of poisons (organophosphates, narcotics, anticholinergics, and salicylates) produce classic clinical patterns.[21] A high index of suspicion, a careful history and physical examination, and appropriate laboratory tests are essential in making an early diagnosis. When eliciting the history, it is important to obtain information regarding the type of poison ingested, the amount taken, the time since ingestion, any antidotes that may have been given, and the presence of any allergies or underlying illnesses. The physical examination should include vital signs, a careful search for trauma, and a good neurologic examination. Reassessment should be done frequently. Physical clues to specific types of poisoning should be sought, e.g., pupillary response and breath odor. Baseline laboratory data should include a complete blood count, serum electrolytes and osmolarity, serum glucose, arterial blood gas with oxygen saturation, clotting studies, urinalysis, and electrocardiogram (Table 1). Maintenance of an airway and adequate tissue perfusion along with frequent monitoring of vital signs and nonspecific therapy are frequently all that is required in most overdoses. The need for more specific therapy should be based on the patient's clinical condition and the results of toxicologic screening.

TOXICOLOGIC SCREENING

The utility and reliability of data obtained from toxicologic screening remains a subject of much debate.[23, 36–38, 44, 57, 94] Toxicologic screening probably should be performed in all patients who are comatose, have changes in mental status, or have a clinically suspected overdose.

Toxicologic screening has several significant limitations.[34, 38, 44] Although it has fairly good specificity, the sensitivity is poor, and the predictive value of a negative test is reported to be approximately 40%.[21] The Centers for Disease Control studied the reliability of 13 laboratories in detecting drugs in the urine and found that a substantial number of drugs were missed.[34] In another study the detection of drugs in the serum and urine of 20 overdosed patients was compared among four laboratories, including one academic research facility. The study found that these laboratories did not reliably identify the overdosed drug, perhaps due to technical limitations, laboratory error, or inadequate specimens.[44] Toxicologic screening is expensive; routine urine and serum toxicologic screening in one laboratory costs $70.00 and $291.00, respectively (National Health Laboratories, verbal communication, 1990).

Table 1. *General Laboratory Clues for Specific Overdoses*

- ELECTROCARDIOGRAM
  - Ectopy
    - Sympathomimetics
    - Tricyclics
  - AV block
    - Digoxin
    - Beta-blockers
    - Calcium channel blockers
    - Cyanide
    - Dilantin
    - Cholinergics
  - Wide QRS
  - Prolonged QT
    - Quinidine
    - Procainamide
    - Tricyclics
- KETOACIDOSIS
  - Ethanol
  - Paraldehyde
  - Diabetes
- KETONES (WITHOUT ACIDOSIS OR HYPERGLYCEMIA)
  - Isopropyl alcohol
- ARTERIAL BLOOD GAS
  - Mixed respiratory alkalosis, metabolic acidosis—salicylates
  - Severe metabolic acidosis—CO* and cyanide
- INCREASED ANION GAP
  - Alcohol
  - Toluene
  - Methanol*
  - Uremia
  - Diabetic ketoacidosis
  - Paraldehyde
  - Iron, isoniazid
  - Lactic acidosis
  - Ethylene glycol*
  - Salicylates, strychnine
- OSMOLAL GAP
  - Methanol*
  - Ethanol
  - Diuretics
  - Isopropanol*
  - Ethylene glycol*

*Important to note because not part of routine drug screen.[13]

Many methods, reviewed elsewhere,[21, 38] are employed to detect toxins. Each method differs in cost, complexity, speed, and accuracy. The practitioner should become acquainted with the particular methods used, their specificity for each drug group, the substances detected by a particular laboratory's screening, and the length of time it takes to obtain results.[21] Justification for the use of toxicologic screening includes the following:

1. Confirmation of the diagnosis, especially in patients whose clinical presentation overlaps many diagnoses. Several studies suggest that the physician's ability to determine drugs ingested accurately is severely limited, even under the best of circumstances.[2, 14, 38, 57, 87]

2. As a guide to therapy. The use of antidotes and forced elimination has inherent side effects making confirmation of the overdosed drug helpful.
3. For allocation of resources. Toxicologic screening can be used to identify abuse and poisoning patterns, therefore, permitting appropriate allocation of manpower, facilities, and types of toxicologic screening that can best serve a particular demographic area.
4. For medicolegal evidence. Toxicologic screening can aid in identifying and supporting diagnoses of abuse and neglect.[14, 23]

Prompt discovery of positive or negative findings on toxicologic screening can eliminate the need for expensive or invasive tests or possibly initiate the search for other causes of a particular presentation. In one study,[36] a group of 200 patients in coma of unknown etiology were referred for toxicologic screening. Greater than 50% were found to have positive screening with the identified substance causally related to the patient's coma.[36] Furthermore, confirmation of toxic levels by quantitative drug testing can initiate or justify the use of specific antidotes or other therapeutic maneuvers.

Several studies have found that the results of toxicologic screening alter therapy in only a small number of patients.[23, 36, 57] Greater than 90% of patients respond with supportive measures and nonspecific therapy alone.[57, 94] When a toxicologic screening is ordered, the sensitivity and positive predictive value may be improved by using an integrated approach. This involves dialogue between the clinician and toxicologist, screening for a wide range of substances, and having reliable data delivered within a short time frame while diagnostic and therapeutic decisions are being made.[38] Many drugs are rapidly metabolized and will have serum levels too low to detect. Therefore, the diagnostic yield is greatly enhanced when both urine and serum specimens are sent.[57]

MEDICAL COMPLICATIONS

When caring for the drug-overdosed patient, it is important to be aware of the complications that may be encountered with the various routes of administration. Bochner et al[11] have presented a very comprehensive discussion of these complications, which we have summarized as follows:

> With parenteral drug use, foreign materials and bacteria can be introduced into the bloodstream. Adulterants, such as talc, may cause organ damage by granuloma formation. Endocarditis is a well-known complication of intravenous drug use that most commonly affects the tricuspid valve and can give rise to septic pulmonary emboli. *Staphylococcus aureus* is the most common bacterial cause of this type of endocarditis, but gram-negative bacteria and fungi also can be causative organisms. Other infections associated with parenteral drug use include cellulitis, abscess formation, necrotizing fasciitis, septic arthritis, and osteomyelitis. Vascular lesions, such as thrombophlebitis, aneurysms, and pseudoaneurysms, also can be seen. Vasculitis can occur, causing ischemia and, possibly, infarction of the affected organ. Tetanus and wound botulism also have been reported and necessitate aggressive therapy. Finally, parenteral drug use is a significant contributor to the spread of acquired immunodeficiency syndrome (AIDS) and hepatitis.
>
> Intranasal administration of drugs is associated with irritation, hyperemia, rhinorrhea, and sinusitis. Cocaine is further associated with mucosal atrophy and septal necrosis. Inhalation of drugs can cause inflammation of the airways and pulmonary fibrosis. Pneumothorax, pneumomediastinum, and pneumopericardium have been reported with forceful inhalation of drugs.
>
> Persons who ingest drugs for illegal transport are at risk for gastrointestinal obstruction and massive drug absorption.

THERAPEUTIC MANEUVERS

The initial treatment of patients with drug overdoses should involve the stabilization of vital signs and the administration of nonspecific antidotes, such as naloxone, glucose, and thiamine. The use of a specific antidote reduces toxicity by decreasing the concentration or blocking the action of the toxin at its effector site.[56] Some antidotes cause serious adverse reactions, and their risks and benefits must be weighed carefully. The following antidotes are now considered obsolete[21]: mineral oil cathartics which, when aspirated, may cause chemical pneumonitis; the "universal antidote," which contains tannic acid, now replaced by activated charcoal; fluid extract of ipecac, which is 14 times more potent than syrup of ipecac and associated with fatalities; apomorphine, associated with fatalities secondary to central nervous system (CNS) and respiratory depression and protracted vomiting; levallorphan and nalorphine, which are more dangerous and less effective than naloxone hydrochloride (Narcan); copper sulfate and sodium chloride solution, which have been replaced by ipecac; and, finally, oral dilution with water, which can actually increase the absorption and toxicity of certain drugs and is only used with corrosive agents when milk is not available.

Extracorporeal Drug Removal

Extracorporeal drug removal (ECDR) is a broad term that includes hemodialysis, hemoperfusion, peritoneal dialysis, continuous arteriovenous hemofiltration, and plasmapheresis. ECDR has a limited application in patients with drug overdose.[21, 27, 30, 57, 98] For most patients, conservative management is all that is required. The adaptation of this approach over the past 40 years has been associated with a significant reduction in mortality and morbidity.[57]

All methods of ECDR are dependent on the vasculature's ability to deliver the drug to a site of removal.[71] Many criteria determine the dialyzability of any drug. First, to be dialyzable, a substance should have a small volume of distribution (V_d). Drugs with a large V_d are not easily dialyzable because only a small amount of the drug is in the vascular compartment at any given time. Second, the substance should have a small molecular weight. High molecular weight compounds cannot cross the pores of dialyzing membranes. Third, the substance should be water soluble. Drugs that are poorly soluble cannot diffuse into dialysate solutions. Fourth, substances should have little or no protein binding because protein-bound drugs cannot diffuse through dialyzing membranes.

Peritoneal dialysis necessitates the presence of an intact gut, requires minimal personnel, and can be started quickly. It is, however, the most inefficient form of ECDR and is rarely used.

Hemodialysis involves the removal of metabolic wastes and other substances across a semipermeable membrane. This is more effective than peritoneal dialysis and is useful in certain life-threatening intoxications, such as with methanol, ethylene glycol, and salicylates. The disadvantages of hemodialysis are the need for reliable vascular access and the use of anticoagulation.

Hemoperfusion involves the passage of whole blood over a charcoal or resin matrix, permitting the adsorption of the drug to this matrix. Hemoperfusion is faster than hemodialysis and permits better removal of substances that are protein bound or are poorly soluble. With the advent of microencapsulated charcoal and resin filters, the side effects of embolization of absorbent particles, destruction of cells, hypothermia, hypocalcemia, hypotension, and thrombocytopenia have decreased but still exist.[15] This procedure also necessitates anticoagulation.

Plasmapheresis is a seldomly used method similar to exchange transfusion except that blood components are returned to the patient. It is less efficient than hemoperfusion and hemodialysis but works with highly protein-bound drugs that have small volumes of distribution.

Continuous arteriovenous hemofiltration has to date been used infrequently for the removal of toxins. Because it is a continuous process and removes large amounts of fluid, it can remove a substantial amount of drug.[13, 27, 32] Further study is needed in this area.

Drugs for which ECDR has been helpful are isopropyl alcohol, methyl alcohol, ethylene glycol, salicylates, lithium, and theophylline.[27]

Alcohols, including isopropyl alcohol, ethylene glycol, and methyl alcohol, produce systemic symptoms after ingestion similar to those from ingestion of ethanol. These symptoms include loquaciousness, discoordination, slurred speech, and lethargy. Coma and seizures can occur. Isopropyl alcohol is twice as potent as ethanol and produces gastric irritation and vomiting. The risk of aspiration is significant. Acetone is a minor metabolite of isopropyl alcohol causing ketosis without significant acidosis. Most patients with isopropyl alcohol intoxication respond to supportive care. In the event of prolonged coma, hypotension, myocardial depression, tachyarrhythmia, or levels of alcohol greater than 400 mg/dL hemodialysis should be considered. Both methyl alcohol and ethylene glycol produce significant toxicity by virtue of their metabolic by-products. These metabolic by-products cause a significant osmolar gap and an anion gap acidosis. Formaldehyde and formic acid are the principal metabolites of methanol, whereas oxalic, glycolic, and glyoxylic acids are the principal metabolites of ethylene glycol. Methanol poisoning can cause damage to the retina and optic nerve, resulting in transient visual impairment or permanent blindness. Ethylene glycol intoxication can be complicated by hypocalcemia, pulmonary edema, and acute renal failure from oxalate crystalluria. The management of methyl alcohol and ethylene glycol overdose includes removal of residual drug from the stomach, prevention of the formation of toxic metabolites, and removal of the alcohol and its metabolic by-products. Gastric lavage or induction of emesis is only helpful within the first 2 hours after intoxication. Sodium bicarbonate can be used for transient improvement of systemic acidosis. Intravenous ethanol is indicated in patients with levels of greater than 20 mg/dL of either drug to prevent further formation of toxic metabolic by-products. Hemodialysis is very effective in removing both the metabolites and the parent alcohol and in correcting the acidosis in ethylene glycol and methanol intoxication.

Salicylate intoxications are seen less frequently with the increased use of acetaminophen but still occur. Patients who are unable to tolerate the sodium bicarbonate load, who have serum salicylate levels greater than 500 mg/L, who are comatose, or who have severe metabolic derangements should undergo hemodialysis.

Treatment of lithium toxicity depends on adequate renal function. Because of the high rate of mortality and permanent neurologic damage, therapy for lithium overdose should be aggressive. Hemodialysis is indicated when severe symptoms or an underlying renal abnormality exists that impairs excretion.

Theophylline is frequently the culprit in drug overdose. Severe intoxication is marked by nausea, vomiting, abdominal pain, arrhythmias, hypotension, decreased consciousness, seizures, and death. Elderly patients with levels of theophylline greater than 60 μg/mL and all other persons with levels greater than 80 μg/mL should undergo hemoperfusion, especially when severe clinical intoxication and underlying cardiac or hepatic disease are present.

Forced Diuresis

In a few selected drug overdoses, forced diuresis with acidification or alkalinization of the urine enhances drug elimination. Drugs can be removed from the plasma either by filtration or by secretion from the kidney. The proximal tubules can actively secrete a large number of acidic and basic drugs.[71] At this level in the renal tubules, alteration in the pH and enhanced diuresis are helpful. A change in pH causes substances in the tubule to become ionized, thereby decreasing their permeability and permitting them to be eliminated. Acidic drugs are significantly ionized at pHs above their pK_a. Short-acting barbiturates, such as secobarbital and pentobarbital, have a pK_a greater than 8.0, thus, renal clearance cannot be enhanced greatly by alkalination of urine in the physiologic range. In order for these methods to be effective, the drug must have a low protein binding, limited metabolism, high renal clearance, and a low volume of distribution.[21]

Alkaline diuresis is recommended in patients with moderately severe salicylate, mephobarbital, primadone (metabolized to phenobarbital), and phenobarbital overdoses.[15, 21, 71] Sodium bicarbonate administration is preferred over acetazolamide as a means to alkalinize the urine, because acetazolamide can cause a hyperchloremic metabolic acidosis.[15] Complications of alkaline diuresis include pulmonary and cerebral edema and electrolyte and acid-base disorders. Renal dysfunction and congestive heart failure are relative contraindications.[21]

Acid diuresis is achieved by the administration of ammonium chloride or a 0.1 molar solution of hydrochloric acid. It has been suggested for use in phencyclidine (PCP) and amphetamine overdoses, but its use in either case is controversial. Phencyclidine has a large volume of distribution and is 90% hepatically cleared.[33] Amphetamines have a cardiac toxicity that can be enhanced by an altered pH and can cause acute tubular necrosis, eliminating the kidneys as a site for drug removal. Acid diuresis is contraindicated in the presence of myoglobinuria, hepatic dysfunction, or renal dysfunction.[21]

Activated Charcoal

Activated charcoal is effective in enhancing the elimination of certain drugs by one of two mechanisms.[15] When administered in a single dose, it can adsorb drugs that remain in the gastrointestinal tract. When administered in serial doses, it can interrupt enterohepatic recirculation of certain drugs and can produce a gastrointestinal dialysis whereby drugs will "back diffuse" from the serum to the gut lumen along a concentration gradient.[6, 8, 15, 21, 45, 52] Drugs for which multiple-dose activated charcoal has been shown to reduce the half-life include theophylline,[66] phenobarbital,[6, 29, 75] phenylbutazone,[66] carbamazepine,[38] tricyclics,[92] and others.[21, 50, 74, 97] Substances that have the properties of enterohepatic or enteroenteric circulation, limited protein binding, and a small volume of distribution can be removed with activated charcoal.[21, 68, 73] Complications of charcoal administration include electrolyte disturbances secondary to the sorbitol,[92] intestinal obstruction,[77] and pulmonary complications secondary to aspiration.[22]

TREATMENT OF SPECIFIC OVERDOSES

Benzodiazepines

Benzodiazepines are extensively used sedative-hypnotic drugs that may account for as much as one third of all ICU admissions for drug overdose at some institutions.[42] They are used as antianxiety agents, sedatives, muscle relaxants, and anticonvulsants. Benzodiazepines appear to act by facilitating the transmission of a major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).[61, 78] It has been postulated that configurational changes occur in the GABA receptor complex from benzodiazepine binding, which increase the opening time of GABA-activated chloride channels. GABA synthesis, degradation, secretion, and reuptake are not affected by benzodiazepines.[78, 90] The presence of two benzodiazepine receptor subpopulations has recently been confirmed in primates by positron emission tomography scanning.[35] Whether these two benzodiazepine receptor subpopulations represent two distinct receptor subtypes or are just two different conformational states of a single receptor is still unclear. Specific and nonspecific agonist and antagonists of these receptors have been isolated.[35]

Most commercially available benzodiazepines can be given orally and are absorbed within 3 hours. Lorazepam, diazepam, chlordiazepoxide, and midazolam can be administered parenterally. All benzodiazepines are highly protein bound, usually greater than 80%. Most of the drugs are metabolized to long-acting metabolites, primarily an N-desmethylated product. A few newer agents (lorazepam, oxazepam, temazepam, and triazolam), however, do not form long-acting active metabolites, and their pharmacologic actions are not significantly prolonged in the elderly or cirrhotics.[1]

Overdoses of benzodiazepines are manifested by progressive deterioration of CNS function, ranging from confusion to coma. Blurry vision, slurred speech, ataxic gait, and paresthesias can also develop. Cardiopulmonary collapse can occur secondary to a depressed respiratory drive, depressed vasomotor tone with resultant peripheral vasodilatation, or direct myocardial depression. Concomitant ingestion of alcohol with benzodiazepines greatly worsens the incidence and severity of these side effects.

Treatment of benzodiazepine overdoses has generally been supportive. Periodic assessment of vital signs and neurologic status is essential. The use of ipecac is indicated if the patient is alert on presentation, but its administration must be weighed carefully against the possibility of a progressively worsening mental status and the drug's prolonged emetic effect. Comatose patients should be intubated early and undergo gastric lavage. All patients should receive activated charcoal. Hemodialysis is rarely indicated and is of limited value, except in patients who remain unstable despite extensive cardiorespiratory support.[31]

The discovery of nonspecific centrally acting competitive benzodiazepine antagonists may have significant implications in the future. One such benzodiazepine antagonist, Ro 15-1788, has been used to shorten the recovery time from benzodiazepine anesthesia[20, 79, 80] and has successfully ameliorated CNS depression following benzodiazepine overdoses in some recent reports.[47, 53] Larger trials will be needed before this treatment can be accepted widely.

Barbiturates

Barbiturates are potent sedative-hypnotic drugs that have been supplanted largely by benzodiazepines because of their less favorable side-effect profile. A large array of barbiturates are commercially available that are distinguished by their duration of action and composition (oxybarbiturates, thiobarbiturates). Ultra-short-acting barbiturates, such as thiopental and methohexital, are used as intravenous general anesthetics. Long-acting barbiturates, such as phenobarbital, are used principally as anticonvulsants. Barbiturates, similar to benzodiazepines, facilitate GABA neurotransmission, but their sites of action are less selective. Furthermore, animal studies suggest that barbiturates can increase the apparent affinity of benzodiazepines to the GABA receptor complex in a dose-dependent fashion.[60] Barbiturates are weak acids that are well absorbed orally and intramuscularly. They are principally metabolized by microsomal enzymes in the liver and competitively bind to hepatic cytochrome P-450. The presence of barbiturates also stimulates the synthesis of hepatic smooth endoplasmic reticulum. These actions increase the metabolism of not only barbiturates but of many other drugs as well.[33]

Overdoses of barbiturates can lead to profound CNS depression and cardiopulmonary collapse. There is marked impairment in respiratory drive as well as in protective reflexes. Severe life-threatening laryngospasm can occur after barbiturate ingestion. Hypotension can be caused by either direct myocardial depression or impaired vasomotor tone from inhibition of ganglionic transmission. Concomitant use of other sedative-hypnotics, such as benzodiazepines, and alcohol can markedly worsen barbiturate overdoses.

Similar to benzodiazepine overdoses, general supportive care is the treatment of choice for barbiturate overdoses. Early endotracheal intubation should be considered. Activated charcoal is highly effective in reducing the half-life of barbiturates.[6, 28] Alkalination of the urine above a pH of 7.5 also may be helpful, but forced diuresis appears only to be effective for long-acting agents, such as phenobarbital.[10] Charcoal hemoperfusion is rarely indicated but can be effective in patients with phenobarbital overdoses whose conditions deteriorate despite supportive care.[49]

Tricyclic Antidepressants

Tricyclic antidepressants are the most common cause of drug overdose fatalities in the United States.[55] They are effective therapy for endogenous depression and are widely prescribed. The probable mechanism of action of these drugs appears to be the central inhibition of norepinephrine and serotonin reuptake. The usual therapeutic dose of a tricyclic antidepressant is 2 to 4 mg/kg/day, whereas the usual fatal dose is 15 to 20 mg/kg/day. In therapeutic doses, these drugs are rapidly absorbed from the gastrointestinal tract. They are very lipid soluble, resulting in a high volume of distribution—approximately 10 to 50 L/kg. Tricyclic antidepressant levels in myocardial cells are five times greater than serum levels. These drugs are highly protein bound, an event that is very dependent on serum pH and serum albumin concentration. Both hypoalbuminemia and acidemia increase the serum concentration of free tricyclic antidepressants. The metabolism of tricyclic antidepressants occurs primarily in the liver by microsomal enzymes.

Overdoses of tricyclic antidepressants primarily affect the parasympathetic nervous system, the CNS, and the cardiovascular system. Symptoms usually develop within a few hours of the ingestion. Anticholinergic side effects tend to be the earliest as well as the mildest of overdose symptoms. These symptoms include mydriasis, blurred vision, dry mouth, hyperpyrexia, tachycardia, urinary retention, decreased intestinal motility, and acute brain syndrome. More complicated and potentially fatal side effects include seizures, coma, hypotension, arrhythmias, and cardiopulmonary arrest. Hypotension probably results from peripheral alpha-receptor blockade, direct tricyclic antidepressant-induced vasodilatation, or myocardial depression. Tricyclic antidepressants also have a quinidinelike myocardial effect. These drugs cause a slowing of the sodium flux into myocardial cells, particularly in the His-Ventricular portion of the AV node. Electrocardiographic changes that occur with use of tricyclic antidepressants include an increased heart rate, an increased PR interval, and flattened T waves. Prolongation of the QRS and QT intervals also can be seen with tricyclic overdoses. The most common mechanism of death in patients with tricyclic overdose is intractable myocardial depression, ventricular tachycardia, or ventricular fibrillation.[24] Torsade de Pointes from QT interval prolongation[19, 39] and conduction delays with a right bundle branch pattern also have been described.[9]

Given the life-threatening potential of tricyclic antidepressant overdoses, investigators have sought a marker to identify patients at risk for seizures or malignant ventricular arrhythmias. Serum tricyclic antidepressant levels do not consistently correlate or predict serious toxicity, perhaps because these levels represent only a minute fraction of the total body level of the drug.[12] Sinus tachycardia is also an insensitive marker for the development of serious toxicity.[67] This probably relates to the different mechanisms of cardiovascular toxicity that occur with tricyclic overdose. Sinus tachycardia is primarily an anticholinergic effect, whereas ventricular arrhythmias are primarily related to the quinidinelike action of these drugs.[24] The most accurate predictor of patients at risk for arrhythmias or seizures appears to be a limb lead QRS duration greater than 0.10 seconds.[12]

Management of suspected tricyclic antidepressant overdose is mainly supportive. Maintenance of a secure airway by early endotracheal intubation, if necessary, and continuous electrocardiographic monitoring are important. Trazodone, a new antidepressant drug that is chemically unrelated to tricyclic or tetracyclic agents, of note, does not appear to have significant cardiac toxicity and may not necessitate cardiac monitoring during overdoses.[26] Ipecac use should be avoided because changes in mental status and seizures can occur abruptly. Because delayed gastric emptying may result from the anticholinergic effects of tricyclic antidepressant overdoses, gastric lavage should be performed even hours after the suspected ingestion.[31] Activated charcoal strongly adsorbs tricyclic antidepressant drugs and is highly effective in accelerating their elimination.[93] Hypotension should be treated with intravenous saline. If fluid challenges are not effective, norepinephrine is the pressor of choice. Dopamine may be less effective as a pressor because endogenous stores of norepinephrine are frequently diminished by the tricyclic overdose.[96] Generalized seizures complicating tricyclic overdoses have been associated with increased mortality and are often noted immediately before cardiac arrest.[9] The acidemia that results from the seizure may displace the bound drug into the serum and provoke a cardiac arrhythmia. Prompt treatment of the seizure is therefore essential. If the patient is intubated, hyperventilating the patient to maintain an alkaline pH greater than 7.45 should be considered. Diazepam should be administered initially to suppress seizure activity. The patient should then be immediately loaded with a long-acting agent, such as phenytoin at the dose of 15 mg/kg. Phenobarbital and physostigmine are alternative agents for refractory situations. The use of physostigmine is very controversial. Physostigmine rapidly reverses the coma, myoclonus, and extrapyramidal effects seen in tricyclic overdoses, but it has potentially life-threatening toxicity, including bradycardia, seizures, asystole, and death. Its use is limited to management of status epilepticus, coma, delirium, severe hypertension, extreme agitation, or supraventricular arrhythmias.[31]

The management of ventricular arrhythmias is also controversial. Alkalinization of the blood by administration of intravenous bicarbonate to a pH greater than 7.45 rapidly converts ventricular arrhythmias to normal sinus rhythm in animal studies.[70, 85] The duration of this effect appears to parallel the arterial pH changes[85] and may be due to decreased free serum drug level. Alternatively, this effect may be due to an increased extracellular sodium concentration diminishing the drug's local myocardial sodium channel block. Hyperventilation to maintain an alkaline arterial pH is probably also effective. Uncontrolled ventricular arrhythmias should be treated with lidocaine using an intravenous bolus of 1 mg/kg and then a continuous infusion of 2 to 4 mg per minute. Phenytoin can be used as a second-line agent. Type 1A antiarrhythmic agents, such as quinidine, procainamide, and disopyramide, are contraindicated because they exacerbate any intraventricular conduction disturbance caused by the tricyclic antidepressant overdose.

Diuresis, hemodialysis, and hemoperfusion are not helpful in tricyclic overdoses because of the drugs' large volume of distribution.

A recent animal study showed a beneficial effect of tricyclic antidepressant-specific Fab fragments in eliminating amitriptyline.[43] Although this research is at an early stage, it holds promise as a new treatment for tricyclic overdose in the future.

Phenothiazines

Phenothiazine and butyrophenones are commonly used in the treatment of psychotic disorders. Phenothiazines are classified based on their chemistry (aliphatic, piperidine, or piperazine compound), pharmacologic actions, and potency. These drugs are sporadically absorbed after oral administration. They are lipophilic and highly protein bound. Their metabolism is principally by hepatic microsomal enzymes. Their therapeutic effect seems to be related to the drugs' affinity for central dopamine receptors in the limbic system. These drugs also bind strongly to a number of other neurohumoral receptors, including muscarinic cholinergic, alpha-adrenergic, histaminic, and serotonergic. The side effects of phenothiazines and butyrophenones are principally related to the drugs' binding to these other receptors and include sedation (histaminic), anticholinergic side effects (muscarinic cholinergic), and hypotension (alpha-adrenergic). High-potency antipsychotics, such as fluphenazine and haloperidol, have less sedative and autonomic blocking activity but are more likely to produce extrapyramidal side effects (dystonia, akathisia, pseudoparkinsonism). The reverse is true of low-potency antipsychotics, such as chlorpromazine and thioridazine.

Overdoses of these antipsychotic drugs are seldom fatal. Anticholinergic side effects are similar to those experienced by patients receiving tricyclic antidepressants: dry mouth, urinary retention, decreased intestinal time, etc. Orthostatic hypotension can occur from peripheral alpha-adrenergic blockade. Respiratory depression is uncommon, but sedation, coma, and seizures can occur. Chlorpromazine can produce conduction abnormalities, similar to tricyclic antidepressants, but these abnormalities are usually less severe.

Management of phenothiazine and butyrophenone overdoses is generally supportive. Removal of intestinal contents by gastric lavage and placement of a Foley catheter to collect urine are important considerations given the anticholinergic effects of these drugs. Similar to tricyclic antidepressant overdoses, hypotension should be treated with saline fluid challenges and, if necessary, norepinephrine bitartrate (Levophed). Diuresis, hemodialysis, and hemoperfusion are of no benefit because of the large volume of distribution of these drugs.

Cocaine

Cocaine is a naturally occurring alkaloid derived from the leaves of the coca plant, which is indigenous to South America. Illicitly sold cocaine preparations can range in purity from 15 to 60%. A purified form or "free base" cocaine can be prepared by extracting the drug from aqueous alkaline solution with an organic solvent such as ether. This process requires the use of elaborate laboratory equipment and some knowledge of laboratory techniques. In the mid-1980s, the advent of a simplified purification process using baking soda and water led to an accessible illicit inexpensive form of purified cocaine known as crack. The introduction of crack has resulted in a dramatic rise in cocaine intoxication as well as cocaine-related deaths.

Cocaine is readily absorbed from the mucosal surfaces of the nose and gastrointestinal tract with a half-life of several hours. Smoking or intravenous use of cocaine has a half-life of only 60 to 90 minutes. Cocaine is predominantly metabolized by hepatic enzymes and plasma cholinesterases. The drug's half-life is prolonged at high plasma levels. Cocaine has many neurohumoral actions. It has a local anesthetic effect resulting from the inhibition of the sodium current in neural tissues. It inhibits neuronal catecholamine reuptake, which results in generalized sympathetic stimulation. Cocaine causes the release of dopamine centrally and may cause the release or block the re-uptake of serotonin.[62]

Cocaine intoxication results in generalized neural stimulation with profound effects on the CNS and cardiovascular system. The drug's autonomic and neuromuscular effects include tachycardia, hypertension, hyperpyrexia, mydriasis, seizures, tremulousness, respiratory arrest, and cardiovascular collapse. Although the drug's addictive initial manifestation is usually euphoria and a sense of well-being, this is followed by a period of depression that may affect vital medullary centers.[33] Hyperpyrexia from cocaine intoxication is the result of increased heat production from increased muscular activity and decreased heat loss due to generalized peripheral vasoconstriction. Hypertension can result from generalized sympathetic stimulation with increased vascular resistance and increased cardiac output. Severe hypertension due to an overdose of cocaine can be complicated by intracranial or subarachnoid hemorrhages or acute aortic dissection with or without rupture. Arrhythmias are common after cocaine intoxication and may be a consequence of sympathetic stimulation, myocardial ischemia, or myocarditis. The most common arrhythmia associated with cocaine use is sinus tachycardia, but ventricular tachycardia, ventricular fibrillation, accelerated idioventricular rhythm, atrial tachycardia, and asystole have been reported.[5, 63] Catecholamine excess associated with cocaine use can result in a distinct yet nonspecific myocardial injury pattern, with the majority of addicts displaying contraction band necrosis on autopsy studies.[95] Myocardial ischemia and infarction can be precipitated by the increased myocardial oxygen consumption from the hypertension and tachycardia of cocaine abuse, coronary thrombosis, or coronary vasospasm.[51, 69] Myocardial infarction may develop hours to days after the last cocaine use.[62] Ischemia of the kidney, intestine, or extremities also can occur, leading to infarction and gangrene.

Headaches are commonly associated with cocaine intoxication. Migraine headaches can be triggered by a cocaine overdose, but persistent severe headaches should raise the suspicion of intracerebral bleeding and warrant the obtaining of a CT scan of the head and, possibly, a lumbar puncture and cerebral angiogram. Strokes and transient ischemia attacks can occur after cocaine use and differ markedly in their presentation from those in patients who have strokes due to cerebrovascular disease. Strokes in cocaine-intoxicated patients occur at a mean age of 32.5 ± 12.1 years and are hemorrhagic in nature 75% of the time. Approximately two thirds of these cerebral bleeds are intracerebral, whereas the rest are subarachnoid in origin. Angiographic data suggest that a large majority of patients with cocaine-associated strokes have occult intracranial aneurysms or arteriovenous malformations.[38] Cocaine-associated stroke can occur with first time use or with chronic abuse and can follow cocaine use by any route of administration. Seizures following cocaine use are usually tonic-clonic in nature and can occur without warning within 60 minutes of oral or nasal overdoses.

Pneumomediastinum and pneumothorax have been reported after cocaine intoxication, probably caused by the rupture of an alveolar bleb from a forced Valsalva maneuver or coughing. Cardiogenic and noncardiogenic pulmonary edema have been described with cocaine abuse. Rhabdomyolysis can be associated with cocaine abuse because of hyperthermia, muscle hyperactivity, and muscle ischemia from intense vasoconstriction and can lead to acute renal failure.

Management of cocaine intoxication is generally supportive. Placement of a secure intravenous line, periodic assessment of the neurologic status and vital signs, and cardiac monitoring are essential. Agitated patients should be restrained physically and given benzodiazepines or haloperidol. Lethargic or comatose patients should be given intravenous naloxone, thiamine, and a bolus of 50% dextrose, unless hypoglycemia is ruled out by a Dextrostix. A CT scan of the head is indicated in patients who present with severe headaches, recurrent seizures, focal neurologic deficits or who are comatose. Chest pain in patients with cocaine overdose should be evaluated with a 12-lead electrocardiogram and a chest radiograph to rule out myocardial ischemia, myocarditis, pneumothorax, or pulmonary edema.

Cocaine-intoxicated patients should not be given ipecac because seizures can occur abruptly, but activated charcoal should be administered in repeated doses. Intubation should be performed in patients who present while comatose, in a postictal state, or in respiratory distress. Ingested vials of cocaine that cannot be removed by cathartics may necessitate surgical removal.[91]

Hyperthermia greater than 40°C should be treated aggressively with evaporative cooling or a cooling blanket. Refractory hyperthermia may require neuromuscular paralysis. Status epilepticus should be treated with an intravenous benzodiazepine, such as diazepam or lorazepam followed by a load with a long-acting agent, such as phenytoin or phenobarbital. If neuromuscular paralysis is used to control hyperthermia, brain seizure activity may persist unrecognized unless the paralysis is permitted to wane periodically or continuous electroencephalographic monitoring is used. Barbiturate anesthesia should be considered for patients with persistent seizure activity. Severe hypertension can be treated with an intravenous vasodilator such as nitroprusside. Hypotension should be treated with fluids and, if necessary, carefully titrated pressors. Lidocaine can be given to suppress ventricular dysarrhythmia. Intravenous nitroglycerine or calcium channel blockers can be used to treat myocardial ischemia. Beta-blockers must be used cautiously in the treatment of cocaine-related hypertension, myocardial ischemia, or tachyarrhythmias, because uninhibited alpha-adrenergic activity can cause or paradoxically worsen hypertension. Labetalol, an alpha- and beta-adrenergic agent, can be used effectively for a cocaine-related hypertensive emergency. Intravenous hydration, possibly with alkalinization of the blood with sodium bicarbonate, is the treatment of choice for rhabdomyolysis from cocaine intoxication.

Most fatalities from cocaine intoxication occur within the first hour of use and after intravenous administration of the drug. Rapid initiation of care and rapid assessment of cardiac, pulmonary, and neurologic function are therefore essential.

Salicylates

Salicylates are widely used, commercially available antipyretic, anti-inflammatory, and analgesic drugs. Although in 1989 analgesics remained the most common group of drugs involved in overdoses,[55] the incidence of salicylate intoxication has declined over the last two decades. This decreased incidence of intoxication is largely due to two factors: (1) the availability and increasing use of other analgesics, particularly acetaminophen and nonsteroidal anti-inflammatory drugs and (2) the marked reduction in accidental poisoning due to the introduction of child-resistant caps.

Aspirin or acetylsalicylic acid is absorbed rapidly after oral ingestion, predominantly from the small intestine and to some extent the stomach. Slight enhancement of salicylate absorption occurs at higher gastric pHs. After absorption, salicylates are widely distributed throughout the body and are protein bound to albumin. The therapeutic effect of aspirin is largely due to its noncompetitive inhibition of cyclooxygenase, the enzyme that is critical for the production of prostaglandins. Prostaglandins are essential mediators of local inflammatory responses and can stimulate the thermoregulatory center in the hypothalamus to produce fever.[33] Aspirin inactivates cyclooxygenase by acetylating a serine moiety at the active site of this enzyme.[81] Salicylates are metabolized by the endoplasmic reticulum or mitochondria of the liver. At therapeutic concentrations, salicylates are eliminated at rates that follow first order kinetics, but at toxic levels, metabolizing enzymes are saturated and elimination is prolonged.

Salicylate toxicity can cause significant metabolic and neurologic abnormalities. Acute intoxication can cause nausea, vomiting, tinnitus, deafness, lassitude, mental confusion, and tachypnea. If unrecognized or inadequately treated, the overdose can progress to hyperpyrexia, convulsions, delirium, gastrointestinal bleeding, coma, and cardiovascular collapse. Salicylates cause an uncoupling of oxidative phosphorylation that increases the metabolic rate which, in turn, increases oxygen consumption and carbon dioxide production augmenting ventilation. Respiration is also increased by a direct stimulatory effect of salicylates on medullary centers. The increased metabolic rate further results in increased heat production and paradoxically in toxic doses can cause fever, sweating, and dehydration. Salicylates can also directly stimulate the medullary chemoreceptor trigger zone, causing nausea and vomiting. Metabolic abnormalities in salicylate overdoses can progress from respiratory alkalosis from hyperventilation to a compensated respiratory alkalosis to mixed respiratory alkalosis and metabolic acidosis. Metabolic acidosis is the result of three factors: (1) dissociation of salicylic acid derivatives at physiologic pH, (2) vasomotor depression of renal function, and (3) accumulation of organic acids from anaerobic glycolysis due to salicylates' uncoupling effect.[33]

The uncoupling of oxidative phosphorylation disrupts normal carbohydrate metabolism, stimulating glycogenolysis and depletion of liver glycogen stores, which initially causes glucosuria and hyperglycemia but can progress to hypoglycemia, particularly in young children. Metabolic acidosis and the neurologic symptoms associated with salicylate intoxication are manifestations of severe or advanced overdoses and are therefore more common in infants and young children than in adults.[76]

The diagnosis of salicylate overdose is determined by the presence of a serum salicylate level above 300 mg/L. The presence of associated metabolic abnormalities and symptoms should raise the suspicion for this diagnosis.

Management of salicylate intoxication involves decreasing the absorption and accelerating the elimination of the drug. Evacuating the stomach contents within 6 hours of the overdose by ipecac or gastric lavage followed by the early administration of activated charcoal is generally accepted treatment.[76] Activated charcoal appears to be the single most effective agent,[16, 18] but gastric lavage does appear to have a significant synergistic effect with activated charcoal.[16]

Severe overdoses should be treated with vigorous hydration, as much as 2 L/hour, and forced diuresis. Alkalinization of the urine is more effective than forced diuresis and can prevent concentration of the drug in vital organs, but salicylates are almost maximally ionized in normal physiologic pH ranges.[40] In addition, vigorous hydration can be complicated by pulmonary edema, either cardiogenic or noncardiogenic. Life-threatening intoxication (serum salicylate level greater than 500 mg/L) may necessitate hemoperfusion or hemodialysis. Of these two modalities, hemodialysis is preferable because it also corrects the metabolic abnormalities associated with salicylate intoxication.

Acetaminophen

Acetaminophen is a commercially available, widely used analgesic and antipyretic agent. Unlike aspirin, it has no anti-inflammatory or antiplatelet activity. The drug is very safe at therapeutic doses but can cause potentially life-threatening hepatotoxicity with overdoses of more than 15 g. Renal failure and hemorrhagic pancreatitis also have been associated with acetaminophen overdoses.[17] Over the last 10 years, a sharp rise in the number of acetaminophen overdoses has resulted from the drug's increased availability and popularity.

Acetaminophen is readily absorbed from the small intestine after oral administration. At therapeutic doses, the drug has an onset of action within 30 minutes and a duration of action of about 4 hours. The drug is sparsely protein bound but widely distributed in tissues. Hepatocytes, in which the drug is principally metabolized, avidly take up acetaminophen into their cytoplasm. Ninety percent of the ingested drug is converted to inactive glucuronide and sulfate conjugates in the liver. The remaining 10% of the drug is either excreted unchanged in the urine or metabolized to mercapturic acid and cysteine conjugates. This latter minor metabolic pathway utilizes glutathione as an intermediary substrate and hepatic cytochrome P-450-dependent mixed function oxidases as enzymes. A highly reactive arylating compound is generated during this process that can bind with hepatocyte protein macromolecules and cause hepatocellular necrosis. This reactive intermediate, however, is usually detoxified by conjugating with cellular glutathione via a pathway catalyzed by glutathione-S-transferase. When glutathione reserves in the liver are depleted to less than 70% of normal values by an acetaminophen overdose, hepatotoxicity begins to occur.[54, 82] The presence of P-450-dependent reactive metabolites stimulates the increased production of glutathione-S-transferase, and a significant rise in this enzyme after acetaminophen ingestion may serve as a marker for those patients who are at risk for hepatic damage.[4] Certain drugs, such as barbiturates, antihistamines, and dilantin, induce the production of these cytochrome P-450-dependent mixed function oxidases and can enhance reactive metabolite production. Cimetidine, which inhibits these mixed-function oxidases, has been shown to have a hepatoprotective effect in animal studies.[88]

The clinical course of a patient who has ingested a toxic dose of acetaminophen can be divided into four stages[83]:

Stage I—mild gastrointestinal symptoms occurring within the first 16 to 24 hours after ingestion.

Stage II—a latent period usually lasting 1 to 2 days after ingestion. Toward the end of this period, hepatomegaly and right upper quadrant tenderness may develop.

Stage III—At 72 to 96 hours after ingestion, mild jaundice and mild gastrointestinal symptoms, such as nausea, vomiting, and anorexia, may develop. Although the magnitude of serum transaminase elevation has little predictive value, elevations of total bilirubin greater than 4 mg/dL and a prothrombin time greater than twice normal values are poor prognostic signs.[54]

Stage IV—Usually by the end of the first week, a gradual resolution of the hepatotoxic episode is seen, although resolution may take longer. If death is averted, liver function usually returns to normal. Chronic hepatic dysfunction has never been reported secondary to acute acetaminophen-induced hepatotoxicity.

When an acute ingestion of acetaminophen is suspected, a serum drug level should be obtained between 4 and 24 hours after the ingestion. A serum level of acetaminophen within 4 hours of the ingestion is difficult to interpret because the absorption and tissue redistribution of the drug is still in progress. The serum acetaminophen level correlates well with the possible risk of subsequent hepatotoxicity if the time from the actual ingestion is known. Nomograms to determine this hepatotoxic risk have been constructed and are widely available.[54, 82, 83]

All patients with suspected acetaminophen overdoses should be given ipecac. If a serum acetaminophen drug level shows the patient to be at risk for hepatotoxicity, N-acetylcysteine should be given. N-acetylcysteine is a commercially available mucolytic agent that has clearly been shown to be hepatoprotective during acetaminophen overdoses.[86] The drug's mechanism of action is unknown, but it may be converted to cysteine, a precursor of glutathione, in hepatocytes. In a large national multicenter study, only 6.1% of patients at probable risk for hepatotoxicity experienced significant transaminase elevations when N-acetylcysteine was given within 10 hours of the acute ingestion. Furthermore, N-acetylcysteine showed hepatoprotective benefit if administered up to 24 hours after ingestion.[86] N-acetylcysteine tastes and smells like rotten eggs and must be diluted to a 5% concentration with juice or soda to be made more palatable. Within 8 hours of the overdose, if possible, a loading dose of 140 mg/kg of N-acetylcysteine should be given followed by 70 mg/kg of N-acetylcysteine every 4 hours for 17 more doses. Although activated charcoal has not been advocated in instances of suspected acetaminophen ingestion,[83] a recent study suggests that activated charcoal in neutral and acidic media adsorbs acetaminophen much more than does N-acetylcysteine.[84] This study justifies the use of activated charcoal alone or together with N-acetylcysteine in mixed overdoses and in unsuspected acetaminophen overdoses before serum levels are obtained.

SUMMARY

The spectrum of drug overdoses seen in the ICU is changing. In 1983 the National Institutes of Health Consensus Development Conference stated that treatment of acute respiratory failure due to drug overdose was one of the most beneficial uses of an ICU. Since that time, however, the incidence of narcotic abuse has declined, and the illicit use of cocaine has risen. Acetaminophen, tricyclic antidepressant, and antianginal drug overdoses have also increased. End organ complications associated with drug overdoses are becoming more common, and the management of the drug-overdosed patient is becoming more challenging.

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Care of the Patient with Brain Injury

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The incidence of head injury is approximately 300 per 100,000 population.[42, 69] It most frequently affects young and otherwise healthy individuals.[2, 36, 42, 71] In all age groups, males are affected two to three times more often than females, and this is especially true between the ages of 15 to 24 years.[2, 15, 36, 42] Importantly, not only are males more frequently affected, but they also have more severe head trauma. Overall mortality with head injury as the prime lethal factor approaches 45,000 deaths annually.[45] The expense to society due to both direct medical expenses and indirect costs from the loss of future productivity remains enormous.[53]

Motor vehicle accidents are involved in more than 50% of all head injuries and in greater than 70% of fatal head injuries.[36, 40, 42] This is particularly true in the pediatric population, with greater than 90% of all severe head injuries related to motor vehicle accidents.[2] More than 50% of patients with severe head trauma have multiple injuries, predisposing to significant blood loss and arterial hypotension, as well as chest and lung injury and hypoxia.[69] Domestic accidents account for a large proportion of head injuries overall (40%), especially mild-to-moderate injuries (40–50%), but they account for a much smaller percentage of severe head injuries (21%).[73] Other causes of head injury include work-related and sports injuries as well as physical assault.[2, 73] Alcohol[23, 73] and illicit drugs are also commonly involved in head trauma. A seasonal variation in the incidence is seen, with an early peak occurrence in April followed by a general increase to the highest monthly percentage in September.[40] Most of these injuries occur on Fridays, Saturdays, and Sundays, thus, placing a large burden on hospitals and trauma units at times when they are usually staffed at a minimum.

The elderly comprise another high-risk group for head injury. In this population, head injury is commonly due to falls. Males again predominate, with an incidence 2.5 times greater than that of females.[42]

The universal application of the Glasgow Coma Scale[98] and the Glascow Outcome Scale[35] permits comparison of the severity of injury between patients[105] and institutions, as well as outcome prediction.[2, 42] The prognosis after head injury depends on the type of lesion sustained,[25] the age of the patient,[2, 7] as well as the severity of the injury (as indicated by the Glascow Coma Scale).[2, 25, 37, 42] For any given lesion and Glascow Coma Scale rating, the elderly have a poorer outcome than do younger patients (age greater than 4 years). The number of patients with a good outcome decreases linearly with age, and the mortality rate increases linearly with age.[2] This is particularly true for those patients with diffuse head injury.[2, 7] In all patients sustaining severe head injury (Glascow Coma Scale rating less than 8 for greater than 6 hours), the presence of an intracranial surgical mass lesion has been associated with a poor outcome, regardless of age.[2, 25] Acute subdural hematoma and diffuse injury with coma lasting longer than 24 hours are associated with the highest mortality and poorest overall outcome. Acute subdural hematoma is responsible for 45% of all deaths due to head injury, with a good-to-moderate recovery in only 22% of these patients. These rates are 32% and 45%, respectively, for patients sustaining diffuse head injury and coma lasting longer than 24 hours.[25] Individually, 61% of all patients with acute subdural hematoma die from their lesion, whereas the mortality rate in patients with diffuse head injury and coma present more than 24 hours is 36%. Unfortunately, these two lethal lesions tend to be among the most common in patients with head injury, with an incidence of 29% and 36% for acute subdural hematoma and diffuse injury, respectively.[25]

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The occurrence of increased intracranial pressure (greater than 20 mm Hg) associated with severe head injury also relates to morbidity and mortality.[20, 71] No difference exists between pediatric and adult patients. Patients with intracranial pressure greater than 20 mm Hg refractory to treatment have overall the worst outcome. Mortality exceeds 90% in both pediatric and adult patients.[2]

Greater than 60% of deaths due to head trauma occur before hospital admission. Of those patients surviving long enough to be admitted, the overall case fatality ratio (number of deaths/number of injured) is low (approximately 3%).[42] Although the number of out-of-hospital deaths can be reduced significantly with early airway and circulatory management,[43] clearly, the major emphasis to reduce morbidity and mortality in this area must focus on preventative measures. These include education on alcohol consumption and the use of illicit drugs while driving. Other efforts should include legislation to increase the legal drinking age, universal application of seat belt and helmet laws, and reduction of highway speed limits. Special educational efforts should be directed at participants in boxing and horseback riding and those persons who use all-terrain vehicles.[39, 44, 103]

For those victims who survive long enough to be admitted to a hospital, the primary management goal focuses on prevention of secondary cerebral injury.[8, 69, 70] If the initial injury is not fatal, presumably subsequent neurologic damage and systemic complications should be preventable in a large proportion of patients.[19, 70, 88] With early intervention by trained personnel at the scene of the injury and rapid referral to a center equipped to treat patients with severe head injuries, a significant decrease in mortality should be accomplished.[2, 27, 71, 73] This is especially true for those patients with intracerebral hematomas.[90, 97] However, the overall mortality rate for patients with severe brain injuries remains in the range of 30% to 40%, emphasizing the overwhelming importance of preventative measures as the primary means of decreasing mortality from severe head injury.[87]

INITIAL MANAGEMENT

Initial management of the patient with head injury should focus on the A's, B's, and C's of resuscitation. Breathing abnormalities occur frequently,[22, 82] with apnea commonly observed in the first minutes following injury.[49] In addition to causing direct hypoxic damage, apnea can predispose the victim to the development of atelectasis and severe ventilation/perfusion mismatch as well as pneumonia.[41, 46, 86] As a result, as many as 50% of these patients have significant arterial hypoxemia on admission to the hospital.[70, 85] The injured brain is particularly sensitive to hypoxia.[32, 34, 70] Therefore, administration of supplemental oxygen and maintenance of a patent airway and regular respirations remain core to the initial phase of treatment. Hypercarbia, which also accompanies hypoventilation, can cause cerebrovascular dilatation with concomitant deleterious increases in cerebral blood flow and intracranial pressure. In fact, hypercapnia at the scene of the accident and on admission to the hospital correlates with the severity of head injury.[85] Therefore, intubation and hyper-ventilation should commence early. In one report,[27] mortality significantly increased if the decision to intubate was delayed for an hour or more (25% versus 38%). It is much more advisable to intubate a patient with marginal indications for respiratory support electively than to risk a delay with potentially catastrophic consequences.

Concomitant injuries can make intubation difficult, and great care must be taken when choosing the method of intubation. Fifteen percent of patients with severe head injury have an associated cervical spine injury.[30] It is mandatory that cervical alignment via axial traction be maintained during emergent intubation. If possible, the presence of cervical fractures or dislocations or both should be determined before attempted intubation. Studies should include lateral cervical-spine radiographs and, if possible, a through-the-mouth odontoid view. However, in a comatose or otherwise noncommunicative patient, even if the cervical spine is normal on radiography, ligamentous injury cannot be ruled out (usually indicated by neck pain in the absence of fractures or dislocation). Therefore, maintenance of cervical alignment during manipulation of the head and neck must still be observed. Because cervical injuries occur less frequently than hypoxia, the decision to intubate in a critical situation should not be delayed pending clearance of the cervical spine.

The route of intubation, i.e., nasal versus oral, should take into consideration the condition of the patient as well as the skill of the physician attempting the intubation. A basal skull fracture relatively contraindicates nasal intubation. The physical signs of basal skull fracture can include cerebrospinal fluid (CSF) rhinorrhea, periorbital ecchymosis (raccoon eyes), ecchymosis over the mastoid bones (Battle's sign), and CSF otorrhea. With intact tympanic membranes, oropharyngeal CSF leakage may develop. Close attention should be paid to any watery discharge from the nose or ear. CSF drainage is identified by a positive glucose reaction, which distinguishes it from a serous discharge.

In an awake or partially awake patient, particularly if the patient is uncooperative or combative, it can be difficult to secure the airway. Sedatives or intravenous anesthetics may be needed. Struggling with a patient to secure an airway in this setting can precipitate large increases in intracranial pressure, with the risk of herniation and patient demise. Most clinicians recommend preoxygenation followed by rapid sequence induction with cricoid pressure and maintenance of axial traction as the simplest and most expeditious approach.[9, 10] Because of its potential to increase intracranial pressure,[61] ketamine should be avoided, but almost any other intravenous anesthetic agent can be used depending on the patient's cardiovascular status. Axial traction should be administered before muscle relaxants because muscle spasm may be the only factor stabilizing the bony fragments in a patient with cervical spine injury. The choice of muscle relaxants has been debated. Succinylcholine can cause a rise in intracranial pressure,[62] but with the prior administration of a thiobarbiturate and, if possible, hyperventilation, this rise will be minimal. In the setting of acute airway compromise and the need to perform subsequent neurologic examinations, the benefit of the rapid onset and rapid termination of action of succinylcholine outweighs the possible transient increase in intracranial pressure.

Facial fractures and soft tissue edema can prevent direct visualization of the larynx, and attempted rapid sequence intubation can prove disastrous. In this situation, intubation over a fiberoptic scope may be the safest route. However, the clinician should have previous experience with this method, preferably under more controlled circumstances. Another consideration is cricothyrotomy. Newer methods utilize a Seldenger technique. Tracheostomy should not be a primary method to establish an emergency airway.

Pulmonary edema occurring during the early phase of resuscitation can impair oxygenation. The association of central nervous system trauma with pulmonary edema (neurogenic pulmonary edema) has been described for many years.[99] The mechanism of injury and actual incidence are not clear.[24, 29, 31, 68] However, when it does occur, fulminant pulmonary edema develops within minutes of the initial injury. Because patients do not generally have underlying cardiopulmonary disease, traditional therapies for pulmonary edema are ineffective, and the outcome is frequently fatal.[99]

Once the airway of a patient with head injury has been secured and effective ventilation and oxygenation established, attention should focus on resuscitation of the cardiovascular system. This helps ensure adequate cerebral perfusion. Transient hypotension after head injury is not uncommon.[70] However, sustained hypotension almost always results from hemorrhage secondary to other systemic injuries. These must be sought aggressively and treated appropriately. The traumatized brain is more vulnerable to secondary injury due to poor perfusion or hypoxia than is normal brain tissue.[32, 34] Shock has been associated with an increase in the incidence of death or vegetative status in these patients.[70, 81] The goal in the hypotensive patient with brain injury is maintenance of cerebral perfusion pressure (CPP) between 60 and 120 mm Hg (CPP = mean arterial pressure − intracranial pressure). Head trauma also disrupts cerebral autoregulation.[21, 59] Therefore, the balance between cerebral hypoperfusion and hyperperfusion, with concomitant changes in cerebral blood volume and intracranial pressure, becomes tenuous. Hyperemia and increased intracranial pressure secondary to elevated CPP is as likely to be associated with neuropsychologic dysfunction as is cerebral hypoperfusion.[100]

Treatment of hypotension includes restoration of circulating volume and isolation of the source of hemorrhage. Either crystalloid or colloid solutions can be used during resuscitation without any significant difference in outcome.[18] However, large quantities (more than 1–2 L) of lactated Ringer's solution should be avoided. The relative hypoosmolarity of lactated Ringer's solution can contribute to brain edema and increased intracranial pressure. Additionally, large volumes (greater than 500 mL) of 6% hetastarch have been reported to cause a coagulopathy, possibly resulting in an intracranial hematoma.[18] Substantial blood loss requires transfusion, preferably with crossmatched blood. The optimal hematocrit to maximize oxygen transport capacity is between 30 and 33%.[104]

In contrast to hypotension and shock, a hyperdynamic circulatory state manifested by hypertension and tachycardia often develops in patients with isolated head trauma, especially in young patients.[13] Commonly, the electrocardiogram (ECG) demonstrates prolongation of the QT interval.[75] Other changes are also frequently seen, including fatal arrhythmias.[58] The changes in cardiac function and electrophysiology can be accounted for by the surge of epinephrine that accompanies head injury.[13, 14] The hypertension can be a relatively transient phenomenon but frequently necessitates treatment well into the convalescent period. The choice of pharmacologic agents used to lower the blood pressure in patients with brain injury can affect intracranial pressure. Direct vasodilators, such as sodium nitroprusside and nitroglycerin, because of their tendency to increase cerebral blood flow and intracranial pressure,[63] can be poor choices in the patient with a closed cranium and elevated intracranial pressure. However, if the urgency of the situation warrants their use, the effects on cerebral blood flow and intracranial pressure can be attenuated by reduced administration rates and concomitant hyperventilation. Trimethaphan, a ganglionic blocker, has little effect on cerebral blood flow and intracranial pressure, but its use is limited because of tachycardia and tachyphylaxis. Nifedipine, although a cerebral vasodilator, has been used successfully.[96] Propranolol and hydralazine have been used extensively in the past, but hydralazine is associated with problems similar to those associated with the other cerebral dilators.[84] It also has a prolonged duration of action. More recently, the use of the short-acting beta-antagonist, esmolol, (half-life = 9 minutes) and the mixed alpha- and beta-antagonist, labetolol, (half-life = 5 hours) has gained popularity in the control of hypertension in neurosurgical patients.[26, 48, 79] These two drugs are easy to titrate and have no significant effect on intracranial pressure or cerebral blood flow.[1, 11, 83]

Following initial physical and neurologic examinations, control of the airway and blood pressure, and appropriate therapeutic interventions to control increased intracranial pressure (see next section), the patient is usually evaluated by CT. The exception is the patient with classic signs and symptoms of a rapidly expanding intracranial mass lesion, such as an epidural hematoma. The classic clinical course of these patients consists of rapid deterioration of neurologic status following a lucid interval. If the neurologic status in these patients is rapidly deteriorating, the delay for CT scan can be disastrous, and the patient should be taken directly to surgery for evacuation of the lesion.[4, 74, 88, 90, 91, 97]

The incidence of normal CT scans in patients with severe head injury ranges between 10 and 40%.[52] This discrepancy is due to the timing of the scan, the number of scans performed, as well as variability in exclusion criteria and the definition of a normal scan. Most patients with a normal scan on initial examination, which remains normal throughout the acute phase, have a generally favorable outcome. However, in a large proportion of patients with an initial normal scan severe disability develops, indicating that a normal scan cannot be equated with a good prognosis.[52] In addition, it is well documented that many patients with severe head trauma experience late-appearing intracranial hematomas. In patients in whom intracerebral hematomas develop, requiring surgical removal, only one third of the lesions are detected in the first 6 hours after injury.[93] Regardless of the findings on initial CT scan, any patient who experiences a worsening in neurologic status or who fails to improve should undergo repeat CT scan.

INTRACRANIAL HYPERTENSION

Monitoring and treatment of increased intracranial pressure can aid in the protection of the brain from secondary injury. Although a significant correlation can be demonstrated between the two, it is unclear whether intracranial hypertension causes secondary brain injury or merely indicates the severity of injury. When intracranial pressure increases to such a level that cerebral perfusion becomes inadequate (CPP less than 40–60 mm Hg), ischemia develops, and, in the extreme, cerebral perfusion stops with resultant brain death. Although the causal role of increased intracranial pressure has been debated, more than half of all deaths from head trauma are associated with intracranial hypertension, and raised intracranial pressure seems to be an important factor for mortality in these patients.[2, 37, 69, 70, 71] In severe head injury, an intracranial pressure greater than 40 mm Hg probably has a direct role in brain ischemia and severe neurologic dysfunction or death.[71] An intracranial pressure of less than 20 mm Hg is associated with less morbidity and mortality than that occurring in patients with an intracranial pressure greater than 20 mm Hg.[2, 47, 71] Impairment of cerebrovascular autoregulation can have an important role in contributing to the higher likelihood of ischemia in the patient with head injury and concomitant intracranial hypertension.[50, 51, 106] In the normal state, cerebral autoregulation results in arteriolar dilation from a fall in arterial blood pressure. Autoregulation results in arteriolar dilation from a rise in intracranial pressure that threatens to reduce cerebral perfusion. Thus, elevated intracranial pressure in the patient with impaired autoregulation can reduce cerebral blood flow at levels of intracranial pressure that normally would be well tolerated by the healthy brain with an intact cerebrovascular regulatory system.

The decision to monitor intracranial pressure in a given patient must be made on a individual basis. In patients with a normal CT scan, the risk of catheter-related morbidity (8%) begins to approximate the incidence of intracranial hypertension (13%).[80] Furthermore, in patients with a normal CT scan and only one or none of the following three risk factors: (1) systolic blood pressure less than 90 mm Hg, (2) age over 40 years, and (3) the presence of motor posturing, the risk of developing increased intracranial pressure approximates 4%.[80] Therefore, the risk-benefit ratio must be judged for each patient and the decision to monitor intracranial pressure made on sound clinical and pathologic findings. In a series of 100 patients with severe head trauma in whom intracranial pressure was not monitored, outcome did not significantly vary from that in a comparable series in which intracranial pressure was monitored.[94] With these considerations in mind, it would seem prudent to monitor intracranial pressure in any patient with head injury who is noncommunicative (eliminating the possibility of serial neurologic examinations) or who is found to have an abnormal CT scan or both.

Current intracranial pressure monitoring devices include an intraventricular catheter, a subdural bolt, and a subarachnoid or intraparenchymal fiberoptic catheter. The relative advantages of one type of monitor over another have been discussed in the literature.[76] The intraventricular catheter offers the advantage of the ability to remove CSF as a direct treatment of acute increases in intracranial pressure. The Richmond bolt tends to be less accurate and more prone to failure. Intraparenchymal catheters, a relatively new technology, appear to be relatively easy to place and highly accurate.

When monitoring intracranial pressure, the clinician must remember that the brain is viscoelastic and that a gradient of pressures can exist across brain tissue.[101] Devices used to measure intracranial pressure reflect a generalized intracranial pressure. Therefore, they may not reflect focal tissue pressures at sites of traumatic injury.[95] These sites can be exposed to higher pressures than those reflected by the monitor, and can, in turn, experience significant ischemia or cellular death at an apparently low intracranial pressure. The lack of cerebral autoregulation, combined with the probable existence of pressure gradients around areas of focal injury, likely contributes to the neurologic deterioration that has been observed in some patients when intracranial pressures reach levels as low as 25 mm Hg.[72] Therefore, intracranial pressures of 20 to 25 mm Hg should be the target level of treatment.[80] In patients with basal skull fractures and associated leakage of CSF, any intracranial pressure monitor will yield falsely low values because the drainage of CSF compensates for the increased intracranial pressure until a critical volume of CSF has escaped. At that point cerebral edema may be massive.

Several common methods are used clinically for controlling intracranial hypertension. The head should be in a neutral position without rotation or flexion and elevated approximately 15 degrees. Hyperventilation is a first-line modality. The cerebral autoregulatory capacity of the injured brain is diminished, but some degree of cerebral vasoreactivity to arterial CO_2 remains. The target $PaCO_2$ should be in the range of 25 to 30 mm Hg. Lower levels can produce exaggerated cerebral vasoconstriction and worsen focal ischemia. The major effect of hypocapnia is transient, with the intracranial pressure slowly rising to a stable pressure after 3 to 5 hours. This pressure, however, is usually lower than the original pressure. Fluid management should follow the guidelines discussed previously.

Initial pharmacologic therapy almost always includes the use of a diuretic. Mannitol, 0.25 to 1 mg/kg, can acutely lower increased intracranial pressure in patients with brain injury.[60, 92] Traditionally, the mechanism for lowering intracranial pressure has been thought to be its ability to create an osmolar gradient across the blood-brain barrier, thus drawing interstitial water from the brain tissue.[3] However, recent studies suggest that the reduction in blood viscosity and concomitant cerebrovascular vasoconstriction seen with mannitol administration may be primarily responsible for its ability to lower intracranial pressure.[78] This "blood viscosity-autoregulation" hypothesis is further supported by the relative inability of mannitol to lower intracranial pressure in patients with grossly defective cerebral autoregulation.[77] After administration of mannitol, decreases in intracranial pressure are observed within 10 to 20 minutes and precede the osmotic diuresis, which occurs within 45 minutes.[54] Blood-brain osmolarity equilibrium occurs a few hours after administration of mannitol. Once equilibrium has been reached, mannitol no longer lowers the intracranial pressure; therefore, a continuous infusion is not an effective long-term therapy. Furosemide is also commonly used to decrease intracranial pressure. Its mechanism of action is not clear, but it may decrease the rate of CSF formation.[57] Used together, furosemide and mannitol work synergistically and hasten the onset of intracranial pressure decrease as well as prolong the effect of lower doses of mannitol.[104] In patients in whom intracranial hypertension resistant to the effects of mannitol and furosemide develops, hypertonic saline can be a good alternative, lowering intracranial pressure as well as improving renal function in these patients.[107] The rapid and often profound diuresis caused by these agents necessitates close monitoring of urinary output and serum electrolytes as well as correction of any iatrogenic abnormalities. Barbiturates can decrease intracranial pressure, primarily by a reduction in cerebral blood flow.[64] In the past, randomized studies have failed to show a relationship between control of intracranial pressure by barbiturate coma and outcome.[89, 102] However, a recent study by Eisenberg and his colleagues[20] suggests that in a minority of patients who fail to respond to conventional therapy, high-dose pentobarbital can be an effective adjunctive therapy in controlling intracranial pressure. In addition, barbiturates can be useful for control of episodic acute elevations in intracranial pressure in the operating room or in the intensive care unit. Steroids have been tried in the past, however, no advantages of high-dose dexamethasone therapy on intracranial pressure trends or clinical outcome in the treatment of severe head injury have been demonstrated.[17]

ANESTHETIC MANAGEMENT

Rational anesthetic planning must involve direct communication between the anesthesiologist and the neurosurgeon so that the anesthetic can be tailored to the individual needs of the patient. Premedication is rarely necessary and should be avoided because sedation will impair future neurologic examinations as well as predispose the nonintubated and ventilated patient to respiratory depression and disastrous increases in $PaCO_2$ and the development of hypoxia. Routine monitors, such as ECG, noninvasive blood pressure, pulse oximetry, and temperature, are mandatory. Arterial cannulation and monitoring of direct arterial pressure is considered a routine practice in these patients. The need for central venous access varies from patient to patient. Occult blood loss can be great and unrecognized preoperatively. The hypovolemia can be augmented by diuretic usage. The arterial hypertension that frequently accompanies head injury along with the ability of the healthy vasculature to compensate frequently masks this underlying condition. The true state of hydration may first be realized after the induction of anesthesia, at which time profound hypotension may be observed. Monitoring central venous pressure can be invaluable as a guide to intravascular volume status as well as an aid to determine the adequacy of resuscitation. In older patients, those with marginal cardiopulmonary reserve, or those in whom neurogenic pulmonary edema has developed, placement of a balloon-tipped flow-directed pulmonary artery catheter helps to monitor left ventricular function adequately.

If the intraoperative positioning of the patient involves the head-up position, the possibility of venous air embolism exists. A precordial Doppler monitor for detection of venous air embolism should be utilized.[28] A multi-orifice catheter positioned at the junction of the superior vena cava and right atrium is useful for confirming the proper placement of the precordial Doppler monitor (by rapid injection of agitated saline) and can also be useful for aspiration of air.[12, 66] At our hospital, such a catheter is typically placed via one of the arm veins as described by Cucchiara et al.[16] Should this not be possible or successful, the relative advantages of having this line in place must be weighed against the risks of placing a central venous line via the internal jugular or subclavian route.[33, 66] Intravascular ECG recording from the catheter offers a rapid and reliable method for determining proper placement of the catheter.[5] End-tidal CO_2 monitoring is extremely useful in determining the adequacy of hyperventilation and, along with end-tidal nitrogen, can aid in the detection of venous air embolism.[56]

The choice of anesthetic agents also depends on the condition of the patient as well as the preference of the anesthesiologist. The goal is to maintain cardiovascular stability and to avoid increases in intracranial pressure. All of the inhalational agents can cause increases in cerebral blood flow and increases in intracranial pressure.[65] However, these effects are decreased significantly by the concomitant use of hyperventilation, narcotics, and barbiturates.[65] Therefore, it would seem reasonable that when one of these agents is used, their concentration should be kept to a minimum and a "balanced" technique employed in which narcotics are used to supplement the anesthetic along with concomitant hyperventilation. Thus, aggravation of intracranial hypertension can be avoided as well as the hemodynamic course stabilized. Barbiturates can be used intermittently or as a continuous infusion to aid in controlling intraoperative intracranial hypertension. The narcotic most frequently used in patients at risk for increased intracranial pressure is fentanyl. Recent data suggest that sufentanil may not be the best agent to use in such patients.[55, 67] However, at our hospital, sufentanil is used extensively in patients with intracranial pathology, including those with space occupying lesions, without observed deleterious effects. In addition to the above considerations, meticulous attention must be paid to patient positioning and padding to avoid peripheral neurologic complications that can result from these frequently lengthy procedures.

Emergence from anesthesia can involve either simply transporting the intubated, ventilated, and anesthetized patient to the Intensive Care Unit or rapid awakening of the patient for neurologic examination. The anesthetic technique described previously can provide for either of these situations. Important considerations in this time period are the avoidance of hypertension and coughing on the endotracheal tube because either can lead to significant intracranial bleeding. Labetolol or esmolol can be used to avoid hypertension as mentioned earlier. In addition, if the brain is adequately decompressed, sodium nitroprusside can be used safely for short-term postoperative control of blood pressure. Because of the dangers of nitroprusside toxicity, this agent should be weaned as soon as tolerated by the patient. Coughing on the tube can be avoided by extubation when the patient is neurologically intact and demonstrates an active gag reflex or, conversely, by the administration of supplemental narcotics, lidocaine, or both.

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High-Risk Cardiac Patient

Focus on Vascular Surgery

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Presently in the United States, there are over 10 million people with coronary artery disease (CAD), 4 million of whom have had a previous myocardial infarction. More than 1 million patients with heart disease undergo major noncardiac surgery each year. Consequently, cardiac-related morbidity and mortality are significant factors affecting these patients' surgical outcome.

Although refinements in patient selection and improvements in perioperative care have contributed greatly to the results of vascular operations during the past three decades, myocardial infarction remains the most common cause of death in patients with CAD. This is due, in part, to a greater incidence of occult CAD in patients with symptomatic peripheral vascular disease compared with the general population.[25, 26] Hertzer et al[26, 27] performed routine coronary angiography in patients with peripheral vascular disease and demonstrated a significantly greater than predicted incidence of occult CAD, including triple vessel disease.

This article reviews approaches to reducing cardiac morbidity and mortality in patients undergoing vascular operations. Risk-factor analysis in patients with peripheral vascular disease and screening methods used for the identification of high-risk patients are described. In addition, essential guidelines of perioperative pharmacologic therapy and myocardial ischemia surveillance are discussed. It is hoped that this article may serve as a general outline of perioperative care of the vascular patient.

IDENTIFICATION OF HIGH-RISK PATIENTS

Risk Factor Analysis

One of the most important aspects of the preoperative evaluation of a patient in whom a vascular operation is planned is the assessment of cardiac risk. In 1977, Goldman et al[22] described a multifactorial index to estimate operative risk in terms of cardiac complications. Goldman criteria that have been shown to be associated

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with increased cardiac morbidity include myocardial infarction within 6 months, New York Heart Association Class III or IV cardiac disease, severe aortic stenosis, pulmonary edema, and emergency operation.

The article by Goldman et al sparked increased interest in the preoperative evaluation of cardiac risk in patients undergoing noncardiac surgery. Detsky et al[14] prospectively evaluated patients for cardiac risk before noncardiac surgery was performed and subsequently offered a modification of the initial Goldman classification system. Cooperman et al[10] identified five preoperative risk factors that were found to be associated with postoperative cardiac events after noncardiac surgery: myocardial infarction within 6 months, congestive heart failure, ventricular dysrhythmia, previous cerebral vascular accident, and an abnormal electrocardiogram (ECG).

Many other reports describe clinical-risk profiles that suggest an increased likelihood of perioperative myocardial infarction or sudden death in patients subjected to vascular operation.[5, 12, 13, 16, 25, 30, 42–50, 58] Although high-risk patients include those with previous myocardial infarction, congestive heart failure, angina pectoris, diabetes mellitus, renal failure, and a spectrum of other chronic conditions, the most significant risk factor is a history of prior myocardial infarction. Major operation is associated with 90% mortality when performed during an episode of acute myocardial infarction; the mortality rate decreases to approximately 23% when performed during the 6-month period after a myocardial infarction. If an operation is performed more than 6 months after a myocardial infarction, mortality declines to less than 3%.[49, 52]

Although preoperative risk-profile classification schemes are useful in patients with asymptomatic CAD, their value in patients with asymptomatic CAD is questionable. The realization that occult CAD may be present in a substantial number of patients with peripheral vascular disease has prompted clinicians to search for the ideal preoperative test that would identify patients who pose a prohibitive operative risk because of critical CAD.

Several studies[3, 15, 48] suggest that preoperative testing is most useful in asymptomatic patients with occult CAD. Studies in which routine preoperative coronary angiography was performed in patients who underwent vascular operations revealed critical coronary artery stenosis in 40% to 50% of patients.[26, 27, 57] However, because of the potential risks and excessive expense of routine coronary angiography, most efforts have been directed toward finding better and less invasive tests to screen for occult CAD. A major stimulus for the identification of high-risk patients preoperatively is the ability to perform therapeutic interventions that can result in a reduction in perioperative morbidity and mortality.

SCREENING TESTS

Electrocardiography

One of the simplest and safest preoperative screening tests available to assess cardiac risk in patients in whom a vascular operation is planned, is the resting 12-lead ECG. The focus of the preoperative ECG should be on the detection of previous myocardial infarction. This is usually signaled by the presence of significant Q waves. The presence of Q waves on resting ECG as an indication of previous myocardial infarction has been found to have a specificity ranging from 88% to 98% but a sensitivity of only 33% to 62%.[59]

The presence of significant ST segment depression (greater than 1 mm) on resting ECG also may serve to identify patients at increased risk for cardiac events following vascular operation.[2] Coriat et al[11] found that patients with ST segment depression on preoperative resting ECG who underwent vascular operations were more likely to have episodes of cardiac ischemia perioperatively than those patients with a normal ECG. On the other hand, Carliner,[6] found only a small incidence of perioperative cardiac events in patients with abnormal ECGs.

The use of ambulatory ECG monitoring to detect myocardial ischemia in patients in whom a vascular operation is planned has recently been evaluated as a means of identifying high-risk patients preoperatively.[48] Results using this screening test indicate that the absence of ischemic changes on ambulatory ECG correlates with minimal cardiac risk for vascular operation, although the implications for those patients with an abnormal ECG are less clear.[48]

Exercise Testing

Although ECG monitoring during exercise testing is believed to be an excellent way to detect myocardial ischemia, it is often impossible to perform in patients with symptomatic peripheral vascular disease because of their inability to exercise adequately. The sensitivity and specificity of this screening test in the detection of significant CAD ranges from 56% to 81% and 72% to 96%, respectively, depending on the protocol used. The sensitivity of exercise testing increases with the number of diseased coronary vessels: one diseased vessel is associated with a sensitivity of 40% to 84%; two vessels, a sensitivity of 63% to 91%; and three vessels, a sensitivity of 79% to 100%.[7, 8, 36]

Radionuclide Angiography

Radionuclide angiography with estimation of ejection fraction and detection of wall motion abnormalities has been found to be of significant value in the preoperative assessment of cardiac risk in patients undergoing vascular operation.[33, 46, 47] Using this screening test, Pasternack et al[46, 47] and Lazor et al[34] found that perioperative myocardial infarctions were most common in patients who had a left ventricular ejection fraction (LVEF) less than 35%.

However, an analysis of data from our institution failed to document a difference in the incidence of perioperative cardiac events in patients with and without a resting LVEF less than 35% who underwent lower extremity revascularization.[18] Patients with normal LVEF but underlying CAD were still at significant risk for perioperative cardiac events if subjected to vascular operation.[18]

Dipyridamole Thallium Imaging

Dipyridamole thallium imaging is a safe and sensitive screening test for the preoperative detection of myocardial ischemia in patients scheduled to undergo a vascular operation. This test is based on the pharmacologic effects of dipyridamole, which normally causes coronary vasodilation, and the affinity characteristics of thallium-201, which is rapidly taken up by viable myocardium. Stenotic coronary arteries cannot dilate in response to dipyridamole infusion and, therefore, the blood flow is relatively fixed.

During this study, dipyridamole is infused first, followed by the administration of thallium. Scans are performed at regular intervals. Normally perfused myocardium takes up thallium rapidly. Ischemic myocardium beyond a coronary artery stenosis takes up thallium in delayed fashion. Nonviable (infarcted) myocardium fails to take up thallium. Dipyridamole thallium imaging provides a general assessment of coronary artery lesions and regional areas of myocardial ischemia.[36]

Boucher et al[3] found that patients with myocardial ischemia detected by preoperative dipyridamole thallium imaging had a higher incidence of postoperative cardiac ischemia after vascular operation than patients with normal studies. These investigators suggested that patients with evidence of severe myocardial ischemia on dipyridamole thallium imaging should be considered for coronary angiography with possible coronary revascularization before the performance of any elective major vascular operation. Patients with improvement in left ventricular function and relief of angina pectoris after coronary revascularization can then undergo major vascular operation without increased risk.[17, 39, 51]

Leppo et al[35] and Eagle et al[15] found dipyridamole thallium imaging to be very sensitive for the detection of myocardial ischemia, but its specificity was poor. Eagle et al[15] reported that the addition of clinical-risk factor assessment to dipyridamole thallium testing resulted in improved overall specificity in the identification of high-risk patients. We often perform dipyridamole thallium imaging in our patients in whom an elective vascular operation is planned and have found this screening test to be relatively safe and sensitive.

MANAGEMENT

Preoperative Preparation

The preoperative preparation of high-risk patients in the Intensive Care Unit (ICU) has been suggested as a method of reducing morbidity in patients undergoing cardiovascular operation. Amin and Iberti[1] found that patients with unstable angina, recent congestive heart failure or myocardial infarction, or significant valvular disease benefited most from preoperative ICU admission before cardiac operation.[1]

Some patients also may benefit from preoperative pulmonary artery catheterization and volume loading to maximize left ventricular function, as well as to assure that oxygen demand is being met adequately by oxygen delivery. The concept of "optimization of hemodynamics" has been studied using measurements of cardiac output and pulmonary capillary wedge pressure,[4, 23, 54] but individualized therapy should be emphasized. In addition, the measurement of mixed venous oxygen tension (by analysis of blood samples drawn from a pulmonary artery catheter) is helpful in assessing the results of volume loading, because the maximum achievable cardiac output is not always associated with optimal oxygen delivery and oxygen consumption.

Pharmacologic Therapy

Much of the preoperative preparation of high-risk patients scheduled to undergo vascular operation is focused on the prevention of intraoperative myocardial ischemia. Therapy is usually geared toward the pharmacologic treatment of potential causes of myocardial ischemia. For example, tachycardia and hypertension may be controlled with beta-blockers, which have been shown to have cardioprotective effects.[29, 44] The administration of a beta-blocker to patients who had sustained acute myocardial infarction was shown to reduce infarct size and mortality. Beta-blockers also may be used intraoperatively to treat tachycardia and hypertension.

Other typical therapeutic interventions that may be performed before vascular operation include the treatment of pulmonary hypertension and ST segment changes on ECG.[41] Intravenous nitroglycerin may be useful in patients with elevated pulmonary-artery pressure, as well as in patients whose ST segment changes appear to suggest myocardial ischemia.[40] Coriat et al,[11, 12] reported a reduction in the incidence of intraoperative myocardial ischemia during noncardiac and vascular operations in patients who received low-dose nitroglycerin intravenously. On the other hand, Gallagher et al[20] found this to be of no significant benefit in patients who underwent coronary revascularization.

Calcium channel blockers also have been evaluated as prophylactic therapy for the prevention of perioperative myocardial ischemia. Godet et al[21] found diltiazem useful in decreasing the incidence of perioperative myocardial ischemia in patients who underwent vascular operation, whereas Slogoff and Keats[55] and Chung et al[9] failed to demonstrate a protective effect.

Inotropic agents are frequently used for cardiac support during the perioperative period in high-risk patients.[49] This class of drugs, which includes dobutamine, dopamine, and amrinone, is used to augment cardiac output. Dobutamine has the added advantage of reducing cardiac filling pressures while increasing cardiac output.[53] These drugs may be given simultaneously with other vasoactive drugs to achieve optimal hemodynamic results.

Detection of Intraoperative Myocardial Ischemia

The detection of myocardial ischemia intraoperatively has conventionally been dependent on continuous ECG monitoring. London et al[38] reported that lead V5 is the most sensitive of the 12 ECG leads for the intraoperative detection of myocardial ischemia and that the addition of lead II to V5 enhances the sensitivity of this method. Haggmark et al[24] compared intraoperative hemodynamic measurements, ECG monitoring, cardiokymograms, and myocardial lactate extraction in patients undergoing vascular operation and found that cardiokymograms were the most sensitive indicators of myocardial ischemia.

Smith et al[56] used two-dimensional transesophageal echocardiography to detect acute systolic wall-motion abnormalities during cardiovascular operations; simultaneous ECG monitoring reflected myocardial ischemia in only 25% of the ischemic episodes.

Postoperative Management

The postoperative period remains a critical time. Significant changes in hemodynamics, disorders in cardiac rhythm, and significant fluid shifts are common. Few studies have evaluated postoperative interventions that would decrease the risk of myocardial ischemia. Pasternack et al[45] reported that the postoperative administration of intravenous metoprolol in patients who underwent abdominal aortic aneurysm repair resulted in a significant reduction in the incidence of myocardial infarction, suggesting that postoperative beta-blockade may be beneficial. However, the routine administration of beta-blockers postoperatively in these patients remains controversial.

Postoperative myocardial ischemia surveillance has conventionally consisted of serial ECG monitoring and measurements of serum creatinine phosphokinase isoenzyme and lactate dehydrogenase. Calvin et al[5] suggested that the combination of invasive hemodynamic monitoring (using a pulmonary artery catheter) and echocardiography during the first 72 hours after operation constituted the most ideal method of identifying patients in imminent cardiac danger. In this period, the role of inotropic agents has become more clearly defined.

SUMMARY

The ideal screening test for the detection of patients at increased risk for cardiac morbidity during vascular operations has not yet been developed. Nevertheless, a broad spectrum of preoperative tests are available and include resting, ambulatory, and exercise ECG monitoring, radionuclide angiography, dipyridamole thallium-201 myocardial imaging, and coronary angiography. Any of these tests may be indicated in the asymptomatic patient, depending on the analysis of individual cardiac-risk factors. At present, we perform resting ECG and dipyridamole thallium-201 imaging in most of our patients who undergo vascular operation. Coronary angiography is performed in selected patients in whom evidence of significant myocardial ischemia is found on these or other comparable tests.

Preoperative pharmacologic therapy is directed toward the treatment of potential causes of myocardial ischemia, such as tachycardia and hypertension. In addition, pharmacologic interventions to reverse intraoperative and postoperative myocardial ischemia are equally important. In this regard, constant surveillance for myocardial ischemia in patients undergoing vascular operation is recommended because the presence of some CAD in these patients is the rule rather than the exception.

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Gastrointestinal Crises in Intensive Care

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Not uncommonly, the intensivist, while caring for the patient admitted to critical care areas of the hospital is faced with critical developments in the gastrointestinal (GI) tract or its appended organs. These crises may present as abdominal pain and unexplained change in critical parameters or changes in laboratory functions, suggesting dysfunction of the hepatobiliary system. Familiarity with these commonly encountered situations can help the intensivist make an early diagnosis and prevent the disasters that commonly occur with late diagnoses. Needless to say, any GI disease can develop or exacerbate in the patient hospitalized in the critical care unit. Additionally, a number of primary disorders may indeed lead to hospitalization and care by the intensivist, (i.e., massive gastrointestinal bleeding). The focus of this review, however, is to acquaint the intensivist with acute situations that develop concomintantly during his or her treatment of the acutely ill patient.

ACUTE ACALCULOUS CHOLECYSTITIS

Acute acalculous cholecystitis (AAC), although accounting for only 5% to 15% of cases of cholecystitis, occurs frequently in the intensive care setting because of its association with trauma, burns, nonbiliary surgery, sepsis, multiorgan system failure, transfusion, and total parenteral nutrition. Its high morbidity and mortality (10%–50%) necessitate accurate diagnosis and prompt treatment.

The signs and symptoms of acalculous cholecystitis can vary from those usually associated with calculous cholecystitis to an unexplained fever in a critically ill patient. Typical findings include fever, diffuse abdominal or right upper quadrant

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pain, right upper quadrant tenderness to palpation, and occasionally a right upper quadrant mass (16%–44%).[55, 77] The signs and symptoms may be nonspecific. In some series right upper quadrant pain is reported in 85% of patients,[58] whereas others report only a 33% incidence. This is probably a reflection of the severity of illness in these patients. Confounding conditions such as recent abdominal surgery, altered mental status, and sepsis make reproducibility of these signs and symptoms unreliable. Indeed a significant minority of patients (13%–33%) were asymptomatic.[55, 77]

Laboratory analysis reveals leukocytosis and may include a variety of liver test abnormalities, including elevated alkaline phosphatase (25%–56%),[42, 77] bilirubin, and serum glutamic oxalacetic transaminase.

The difficulty in making a clinical diagnosis has made noninvasive abdominal imaging an important adjunct. Ultrasonography offers the advantage of a portable, readily available diagnostic tool that can be used serially in a critically ill patient. Findings consistent with acute acalculous cholecystitis include thickening of the gallbladder wall of more than 3.5 mm, a subserosal halo of edema, a pericholecystic fluid collection in the absence of ascites, marked gallbladder distention, and hypoechoic areas representing fragmentation within the gallbladder.[11, 33] The presence of sludge is nonspecific because it is a common finding in debilitated patients without oral intake. The sensitivity of ultrasonography ranges from 36% to 84%.[42, 58] The use of hepatobiliary imidodiacetic acid (HIDA) scanning allows functional evaluation of the biliary tract. Findings consistent with acute cholecystitis, but not specific for the acalculous variant, include nonvisualization of the gallbladder with biliary tract to intestinal flow, suggestive of cystic duct obstruction, and absence of biliary tract to intestinal flow, suggestive of common duct obstruction. Fox et al[42] reported a 93% sensitivity with HIDA scans in the setting of AAC. Other authors caution interpretation given the high degree of false-positive scans in fasting, debilitated patients.[43] Other tests of the biliary system are also associated with a high degree of false-positive results: oral cholecystography, 36%; intravenous cholangiography, 38%; and percutaneous transhepatic cholangiography, 33%[42]; these have been replaced by USG and HIDA scanning.

Treatment of AAC includes cholecystectomy or cholecystotomy, the choice of procedure based on overall condition of the patient and extent of gallbladder necrosis. In a substantial number of patients, advanced gallbladder disease is found, including gangrene (40%–78%), empyema (12.5%), and frank perforation (15%–27.5%).[43, 47, 48, 58, 77] In a review by Johnson[58] the importance of early diagnosis of AAC is highlighted. Forty percent of patients who underwent operation more than 48 hours after onset of symptoms were found to have perforation, with its concomitant high morbidity and mortality. In contrast to these results only 8% of those who were treated surgically within 48 hours suffered perforation. Although these patients are clearly a high surgical risk because of their underlying problems, they are in fact too sick not to undergo operation.[55] Perhaps the newer advances in laparoscopic cholecystectomy will provide a suitable, less invasive method for cholecystectomy in this high-risk group.

The histopathology of surgical specimens[48] includes marked edema and focal necrosis of the serosa and muscularis mucosa of the gallbladder. Additionally, focal necrosis and thrombosis of arteries and veins have been seen. Of note, the mucosa—except in areas of gangrene—remains relatively unaffected.

The pathogenesis of AAC has not been fully elucidated. Many theories have been advanced in the literature. Initial emphasis was placed on increased bile viscosity, exacerbated by dehydration, fever, and prolonged fasting, which led to a functional obstruction of flow through the cystic duct.[47] Use of narcotics, notably morphine, with subsequent increase in sphincter of Oddi pressure could also exacerbate depressed gallbladder emptying. Increased bile pigment production secondary to hemolysis with multiple blood transfusions could also change bile composition, as proposed by Lindberg et al[67] in writing about Viet Nam experiences. Another proposed mechanism is mucosal ischemia, seen in many critically ill patients with episodes of hypotension related to sepsis, trauma, and hypovolemia, especially if superimposed on preexisting atherosclerosis. Increased intraluminal gallbladder pressure could also decrease mucosal perfusion, as might be seen with inspissated bile. There have been reports that positive pressure mechanical ventilation increases this intraluminal pressure, perhaps exacerbating mucosal ischemia.[57] Other possible causes include reflux of pancreatic enzymes, cystic duct occlusion from fibrosis or stenosis, or vagotomy-induced stasis.[42]

An interesting theory has been proposed by Glenn and Becker.[48] They have reproduced the histologic injury seen in AAC (vascular disruption and thrombosis in the serosa and muscularis) in experimental animals by activating factor XII (Hageman factor) dependent pathways of coagulation and kinin formation. This pathway can be activated when plasma is exposed to collagen or in response to gram-negative endotoxins, providing a theoretical basis for AAC in settings of burns, trauma, surgery, and gram-negative sepsis. As with AAC, bacteria do not seem to be directly pathogenic and instead may superinfect an already diseased gallbladder. The incidence of positive gallbladder cultures is similar in calculous and acalculous cholecystitis (59% vs 63%) and usually include gram-negative enteric flora, enterococci, and anaerobes such as *Bacteroides fragilis* and *Clostridium perfringens*.[33] As none of these theories fully explain all cases of acalculous cholecystitis, it is best to consider its pathogenesis multifactorial.

CEFTRIAXONE-INDUCED BILIARY PSEUDOLITHIASIS

Ceftriaxone is a parenteral third-generation cephalosporin with a broad antimicrobial spectrum often used in intensive care settings. It has a long half-life allowing daily or twice daily dosing and has a high degree of biliary excretion. Ceftriaxone has been associated with creation of biliary sludge, first incidentally found by Schaad et al[91] on routine ultrasound for a splenic abscess in an adolescent patient. A subsequent prospective study by Schaad et al[92] followed the progress of 63 children after initiation of ceftriaxone therapy; 16 patients (43%) developed biliary concretions, 3 patients (19%) developed symptoms. Follow-up ultrasonograms documented resolution within 2 to 63 days. Jacobs[56] described a case of acute cholecystitis in a 16-year-old patient receiving ceftriaxone, with ultrasonographic documented hyperechogenic material in the gallbladder. Pigran et al[82] documented a 25% incidence of pseudolithiasis in a small series of adults receiving ceftriaxone and they noted an association with large dose and prolonged administration. Analysis of the sludge reveals only small amounts of cholesterol and bilirubin but large amounts of calcium salts.[12] Although not a limiting factor in selecting this antibiotic because of its low rate of symptomatic biliary disease, this effect should be highlighted because of the frequent use of this drug.

PSEUDOMEMBRANOUS COLITIS

Pseudomembranous colitis is defined by the gross or histologic findings of pseudomembranes composed of fibrin and inflammatory cells on areas of mucosal ulceration in the colon. Its association with severe illness and antibiotic usage make it a common finding in the intensive care setting.

The cause of pseudomembranous colitis is now known usually to be *Clostridium difficile* associated with the use of antibiotics. Pseudomembranous colitis was encountered before the use of antibiotics; however, Finney[40] is credited with its first clinical description in 1893. Most nonantibiotic associated cases have been in a postsurgical setting—either colonic, gastric, or pelvic. Additional associated conditions often cited include intestinal obstruction, cardiovascular insufficiency, uremia, spinal fracture, severe infection, heavy metal intoxication, severe burns, Crohn's disease, Hirschsprung's disease, and ischemic colitis.[6, 45, 106] With the advent of widespread antibiotic use in the late 1930s, *Staphylococcus aureus* became the presumed etiologic agent based on stool cultures, gram stains, and response to antistaphylococcal therapy.[45] This cause has subsequently been challenged. In the late 1970s, Bartlett et al,[7] while working with a hamster animal model, were able to elucidate that a cytotoxin of a clostridial species was the cause of a form of pseudomembranous colitis.

Subsequent studies have allowed characterization of a number of *C. difficile* toxins believed responsible for pseudomembranous colitis, which are named toxins A, B, D_1, and D_2.[4, 104] Toxin B is a highly potent cytotoxin to all cell lines examined, which produces disruption of actin microfilaments of the cytoskeleton. Toxin A, although less potent, is also cytotoxic. Its main activity is enterotoxic producing fluid flux and mucosal inflammation. Toxin A is believed to be primarily responsible for clinical disease, whereas toxin B may be a sensitive marker for *C. difficile*.[6] Toxin D_1 is known to cause hemorrhage in ligated rabbit ileal loops and toxin D_2 is strongly cytopathic in He La cell culture.[4, 113] How toxins D_1 and D_2 influence clinical disease is not as well understood as with toxins A and B.

C. difficile intestinal disease is in most cases associated with antibiotic therapy. The most frequently associated antibiotics include ampicillin in 30% of cases, clindamycin/lincomycin in 26% to 28% and cephalosporins in 28% to 55% of cases.[8, 96] All three generations of cephalosporins have been implicated, although first generation cephalosporins are implicated far more frequently than second or third generation. Whereas pseudomembranous colitis has classically been associated with clindamycin, it is important to note the high percentage of cases associated with the penicillin analogues. This must be placed in perspective, given the almost ubiquitous use of these antibiotics in penicillin nonallergic patients. The relative use of clindamycin has also decreased because of this well recognized side effect. In separate prospective trials of 200 patients, Tedesco et al[107] found a 21% incidence of diarrhea and 10% incidence of pseudomembranous colitis associated with clindamycin, contrasted with a 4.5% incidence of diarrhea and 0% incidence of pseudomembranous colitis associated with ampicillin. Therefore, the high incidence of ampicillin and cephalosporin-associated cases probably reflect their widespread use.

In addition to these well described agents, it is clear that pseudomembranous colitis can be associated with almost all antimicrobial agents, including other penicillin analogues (ticarcillin, methicillin, nafcillin, cloxacillin), trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, erythromycin, amphotericin B, and metronidazole.[96] Vancomycin and perhaps parenterally administered aminoglycosides seem not to be clearly associated.[106] Series that include aminoglycosides probably reflect concomitant use of other antibiotics because these agents are seldom used alone. Pseudomembranous colitis with positive *C. difficile* titers and stool cultures has been described without antibiotic therapy.[80] There have been reports of pseudomembranous colitis associated with antineoplastic drugs, including methotrexate, adriamycin, cyclophosphamide, and 5-fluorouracil.[96]

What remains unclear is what factors allow *C. difficile* to become pathogenic. *C. difficile* is found in <3% of normal adults in the United States and Europe, but is commonly found in the intestinal flora of apparently normal neonates without gastrointestinal disease. A number of possible mechanisms have been proposed.[72, 96] First is suppression of normal enteric flora by sterilization with antibiotics. The normal flora may some how suppress *C. difficile* by inhibiting or binding toxin or occupying mucosal sites. Without such homeostasis perhaps *C. difficile* is free to produce disease. Second is the source of *C. difficile.* In the 97% of patients without culturable *C. difficile* in their stool, the organism must be introduced from another source.[72] This could be either endogenous or exogenous. Besides feces, other endogenous sources have included the genitourinary tract. Genitourinary cultures of male and female patients have shown carriage of 0% to 100% for *C. difficile,* perhaps related to culturing techniques.[72] Exogenous sources have included household pets (i.e., dogs, cats, and birds) and foods (although this has yet to be substantiated). Perhaps most important in an intensive case setting is nosocomial infection. There have been reports of clustering of cases in intensive care units among patients who are on multiple antibiotics, are fecally incontinent or require bedpans, and those requiring total nursing care.[41] Third is the ability of *C. difficile* to multiply within the colon, even during antibiotic therapy to which it is susceptible in vitro (i.e., ampicillin). This may be related to the ability of the organism to sporulate, a stage relatively unaffected by antimicrobial therapy. Fourth is perhaps some variation in host susceptibility to the organism or toxin. Finally, there may be more pathogenic strains responsible for disease other than those found in healthy carriers.

The clinical features of pseudomembranous colitis can be varied but classically are associated with prolonged bouts of diarrhea with signs of systemic infection.[6, 106] Although *C.-difficile*–associated pseudomembranous colitis may present as a benign episode of antibiotic-associated diarrhea, this is uncommon. Watery diarrhea is present in 90% to 95% of patients. Although it is frequently hemoccult positive, frank bloody diarrhea only occurs in 5% to 10% of patients. Crampy abdominal pain and signs of systemic infection, including leukocytosis and fever, occur in 80% of patients. Rebound tenderness can occur in 10% to 20% of patients. The temporal relationship to antibiotic therapy can vary; most present during the fourth to ninth day of therapy; however, 25% to 40% of patients can develop colitis 2 to 10 weeks after completion of antibiotics. Reported complications include severe dehydration, electrolyte imbalance, hypotension, hypoalbuminemia secondary to protein losing enteropathy, toxic megacolon, and colonic perforation.[6] Although pseudomembranes have been described in the small bowel, antibiotic associated pseudomembranous disease is confined to either the universal, proximal, or distal colon.[45]

Diagnosis is best made by assay of the *C. difficile* cytotoxin (toxin B). The assay involves cytotoxicity to cell cultures when exposed to fecal extracts, which is subsequently neutralized by clostridium antitoxin. The toxin assay is positive in 83% to 96% of cases of pseudomembranous colitis.[45] Of note, the assay is also positive in 20% of cases of diarrhea where pseudomembranes are not sought or found.[6, 45] In either situation, positive toxin titers correlate well with response to oral vancomycin therapy.

Stool cultures for *C. difficile* are difficult to perform because of a need for highly selective culture media. Although the test is sensitive (89% of patients with pseudomembranous colitis),[45] it is not specific enough (37% positive in diarrhea without pseudomembranes) to provide useful additional information.

Sigmoidoscopy can be used to identify characteristic pseudomembranes, although it adds little to the finding of a positive toxin assay. Because of the possible risk of endoscopy in these patients, it is not universally performed.

Therapy of pseudomembranous colitis is multifactorial. Initial therapy includes discontinuation of any antibiotic drugs with substitution of an alternative regimen if possible, general supportive care, bowel rest, and initiation of enteric precautions for all patients in acute and chronic care hospital settings. Specific therapy can be initiated with oral vancomycin (125 mg orally every 6 hours), oral bacitracin, or oral or parenteral metronidazole. There is extensive experience with oral vancomycin, which is attractive because its lack of absorption from the intestinal lumen and thus lack of systemic side effects. There is a 95% to 100% response rate. Bacitracin (25,000 U orally every 6 hours) has been studied and shown to have equal efficacy with lower cost.[118] Bacitracin is also like vancomycin not absorbed and therefore has no systemic side effects. Metronidazole (250 mg orally every 8 hours or 500 mg intravenously every 6 hours) is the only agent that can be used parenterally for patients who can not tolerate oral medication. The administration route should be changed to oral as soon as possible.

Unfortunately, with any of the three antibiotic regimens there is a substantial relapse rate; in one large series[9] with vancomycin, 24% relapsed and 11% had two or more relapses. These rates are comparable with any of the recommended regimens.[6] Possible causes for these relapses include emergence of a resistant strain of *C. difficile* (although patients usually respond to retreatment with the same agent); spore formation taking place during therapy, allowing proliferation after discontinuation of antibiotic therapy; or recolonization from the environment.[106] Because of the high relapse rate after antibiotic therapy it is often prudent to withhold therapy from patients with mild symptoms who appear to be resolving spontaneously.[6, 10]

In addition to antibiotics, anion exchange resins (cholestyramine or cholestipol) have been used in treatment of pseudomembranous colitis. First described by Burbige and Milligan[21] prior to the understanding of the etiological role of *C. difficile*, subsequent studies revealed that the resins bound the cytotoxins.[118] The clinical experience is varied, with some investigators having excellent results while others document high relapse rates.[10] An additional problem is that the resins also bind vancomycin. This decreases colonic levels but does not appear to effect outcome either positively or negatively.[10] Other alternative therapies have included restoration of normal fecal flora with either lactobacillus preparations or fecal enemas. Finally, in rare instances of fulminant colitis or toxic megacolon complicating pseudomembranous colitis, surgery can be considered.[113]

The therapy of relapses usually involves retreatment with the initial agent. Recurrent relapses require more prolonged therapy with vancomycin or metronidazole followed by therapy with cholestyramine, lactobacillus, or low-dose alternate day vancomycin.[10, 106]

STRESS ULCERS

Acute gastric mucosal lesions associated with physiologic stress (stress ulcers) remain common in critical care settings. Stress ulcers are best defined as "multiple shallow erosions in the fundic region of the stomach in seriously ill patients."[70] Their superficial nature makes perforation and clinically torrential bleeding rare. They are virtually always present in the fundus but can be found in the antrum and duodenum in conjunction with fundic lesions.

The true incidence of stress ulceration probably approaches 100%. A prospective endoscopic evaluation by Lucas et al[68] studied 42 patients who were severely injured. They found fundic mucosal erosions in all patients. Initial lesions included areas of pallor and hyperemia followed by petechia and small erosions within 24 hours of injury. A number of studies have evaluated the incidence of upper gastrointestinal hemorrhage in acutely ill patients. Schuster et al[93] prospectively studied 174 patients admitted to a medical-respiratory intensive care unit. Overt or occult upper GI bleeding occurred in 14%. Without endoscopic follow-up, however, the cause of hemorrhage could not be ascribed with certainty to stress ulceration.

Stress ulcerations occur during periods of physiologic stress and have been associated with major trauma, surgery, sepsis, hypotension, respiratory failure, acute renal failure, hepatic failure, and in patients with coagulopathy. In Schuster's[93] prospective study, a diagnosis of respiratory failure, a malignancy, or sepsis was more common among those who bled. Of the factors tested, a coagulopathy (thrombocytopenia, prolonged prothrombin time or partial thromboplastin time or use of anticoagulants) or need for mechanical ventilation were the most strongly associated with the risk of bleeding.

Two specific clinical settings deserve emphasis. Curling[29] first described acute ulcerative disease of the duodenum in 1842, but the term Curling's ulcer has been expanded to include gastric ulcers as well as more superficial lesions of gastric and duodenal mucosa. In the setting of burns, Czaja et al[32] prospectively endoscopically studied 32 patients admitted to a burn unit. Seventy-eight percent of the patients had acute mucosal disease; 86% of those patients with larger burns (>35% of body surface area) had disease, whereas patients with smaller burns had normal gastroduodenal mucosa. Curling's ulcers seem indistinguishable from other stress erosions; they occurred in the first 72 hours of injury and were most common in the gastric fundus. Actual ulcers usually occurred in areas of diffusely abnormal mucosa and occurred after 72 hours of injury. The authors therefore believed that ulcers represent progression of early erosive disease. Despite their common occurrence, only 5% of these lesions lead to life-threatening hemorrhage. In the setting of central nervous system trauma (accidental or postsurgical) there is also a high incidence of mucosal disease. These are frequently termed Cushing's ulcers, after their description by Harvey Cushing in 1932.[31] They may behave differently than other stress ulcerations. Cushing's ulcers tend to be deep, full thickness lesions of the esophagus, stomach, or duodenum and, hence, have an increased incidence of perforation.[20] Central nervous system lesions have been associated with hypersecretion of both gastrin and gastric acid with obvious etiologic implications. In a prospective study of gastrointestinal bleeding after head trauma to 433 patients, Kamada et al[61] found an overall incidence of bleeding of 17%. There was also a correlation to severity of injury. Conscious patients had a 4% incidence, whereas decerebrate patients had a 42% incidence. Endoscopic evaluation found an overall incidence of 75% of actual mucosal lesions. In a prospective trial of Cimetidine prophylaxis in the setting of head injury, Halloran et al[52] reported a 75% incidence of bleeding in a control group versus 19% in a cimetidine-treated group. One patient who underwent endoscopy was found to have a deep ulcer that subsequently perforated.

The pathogenesis of stress mucosal lesions probably involves a complex interplay between luminal acid, mucosal blood flow, and the maintenance of a gastric mucosal barrier.[70, 95, 117] Most studies agree that both acid and pepsin need to be present to cause mucosal lesions, hence the rationale for antacid or H_2 prophylaxis. Buffering intraluminal acid in animal models leads to decreased incidence of ulceration. There does not seem to be an increase in gastric acid secretion however (other than in Cushing's ulcer), making local tissue factors important. Of prime importance is mucosal ischemia, easily produced in periods of physiologic stress. This tissue ischemia may limit the ability of the mucosa to dispose of the small amount of H^+ that normally diffuses back through the mucosa or secretes mucus and HCO^3, which establish a protective barrier. In addition, HCO^3 within the mucosal cells may play an important buffering role. HCO^3 produced from the blood side of the oxytocic cell, the "alkaline tide" may also protect the mucosa. Other local tissue factors, including rapid epithelial renewal and tissue mediators such as prostaglandins and leukotrienes, also afford surface protection.

Whereas the incidence of stress mucosal lesions is high, as proven by endoscopy studies, the actual incidence of frank gastrointestinal hemorrhage is only approximately 5%.[70] The mortality associated with stress ulcer bleeding can be from 12% to 50%[70, 117] and is usually associated with progression of underlying disease. Significant hemorrhage, when it occurs, is best evaluated endoscopically. This allows not only the thorough evaluation of the entire mucosa to identify a bleeding site but allows the identification of other unsuspected lesions (i.e., undiagnosed peptic ulcer disease or neoplasm). As a rule, barium studies are not indicated. They are technically difficult in these critically ill patients and are unable to identify shallow mucosal defects.

Treatment of acutely bleeding lesions involves a general approach to supportive care and aggressive attempts at reversal of the underlying physiologic stress, especially correction of sepsis, hypotension, or coagulopathy. Occult bleeding (i.e., guaiac positive nasogastric aspirate) usually is nonprogressive.[117] Gross bleeding can generally be prevented by raising the intraluminal pH with antacid therapy. Curtis et al[30] showed control of bleeding in 70% of 23 patients with frank hemorrhage through a nasogastric tube and in 89% of 49 patients with endoscopically proven hemorrhagic gastritis[97] by raising the intraluminal pH to more than 7 with antacid therapy. Similar results were found by Dunn et al[34] in a small series of patients treated with cimetidine. Ongoing bleeding despite therapy with antacids and H_2 blockers requires an aggressive approach with a variety of therapies, including endoscopic coagulation with heater probe or laser, angiography with embolization or infusion of vasoactive substances, or as a last resort, surgery.[70] The mortality of such surgery is from 30% to 75%.[70, 117]

The understanding of the high incidence of stress ulceration and its small, albeit significant, risk of serious complications has led to the widespread use of prophylactic therapy to prevent progression of stress ulcer disease in the critically ill. Prophylactic therapy for prevention of stress ulcer bleeding is based on three premises: (1) morbidity and mortality related to stress ulcer syndrome are significant; (2) the population at risk can be identified prior to bleeding; and (3) therapy that decreases gastric acidity or improves gastric mucosal defense mechanisms prevents ulcer formation or progression to bleeding.[121] One would also have to consider the relative risk of prophylactic therapy because no medical therapy is risk free. The risks of prophylaxis would have to be outweighed by its benefits. There have been a plethora of studies of prophylactic therapies utilizing antacids, histamine receptor antagonists, sucralfate, and newer agents such as misoprostol. The review of these data is beyond the scope of this article but is reviewed by Wilcox and Spenny[117] and Zuckerman and Shuman.[121] A number of points deserve emphasis. Antacids have long been considered the gold standard of therapy, with clear prophylactic benefit. Hastings published an early study comparing antacid titration to a pH >3.5 versus no prophylaxis in 100 intensive care unit patients and found a 4% versus 24% bleeding rate in the respective groups. Antacid therapy is labor intensive, however, requiring frequent pH monitoring and often large doses of antacids (up to 120 mL per dose), with subsequent diarrhea or electrolyte abnormalities; hence, the appropriate enthusiasm for the use of H_2 blockers, cimetidine, and ranitidine, which afford ease of administration. H_2 blockers have been shown to be efficatious prophylactically when compared to placebo.[81] The theoretical drawback to H_2 blockers is that actively secreting gastric mucosa is more resistant to ulceration, perhaps because of the HCO^3 secreted, and therefore, they may not be as efficacious as antacids. Studies comparing antacids directly with cimetidine have shown an advantage to antacid therapy.[84, 119] A recent review[121] of available studies highlights that the advantage is only significant in prevention of occult bleeding; when prevention of clinically significant bleeding is the goal there is equal efficacy with antacids and H_2 receptor antagonists. Recent studies have also reviewed the use of continuous infusion H_2 blockers as a method of maintaining gastric pH >4 consistently instead of intermittently, as seen with bolus therapy.[63, 78] Sucralfate, an aluminum salt of sucrose octasulfate, has also gained widespread acceptance. Its mechanism of action is through mucosal protection by binding to surface proteins and adsorbing bile and pepsin, and by stimulating prostaglandin synthesis. It is not absorbed and does not inhibit gastric secretion. Borrero et al[19] studied 155 patients and found similar rates of bleeding (all occult) in sucralfate and antacid-treated patients (2.8% vs. 2.6%), with obvious administration advantages with sucralfate. Increasing understanding of the role of prostaglandins has lead to the investigation of misoprostol, a prostaglandin E1 analogue, as a possible prophylactic therapy.[120] This has not as yet received widespread acceptance.

Note should be made of the possible complications of prophylactic therapy because they are not risk free.[110] Alkalinization of gastric juice with antacids or H_2 blockers has been associated with colonization with gram-negative organisms and a higher incidence of aspiration pneumonia and systemic infection. H_2 blockers have well-known side effects such as neuropsychiatric disturbance, thrombocytopenia, increased serum creatinine, and interaction with many drugs commonly used in the critical setting, such as aminophylline and lidocaine. The presence of H_2 receptors in the heart also raises the possibility of bradycardia and negative ionotropic effects in the setting of H_2 blockade. Obviously, stress ulcer prophylaxis should not be used indiscriminately.

The overall recommendations regarding stress ulcer prophylaxis obviously remain controversial. It seems reasonable, however, to undertake prophylactic therapy in patients with known risk factors as previously outlined. The type of therapy can be individualized for each patient but can include regimens of antacids, H_2 blockers, or carafate, as outlined by Wilcox and Spenny.[117] Patients without risks can safely be followed, and therapy can begin should stress mucosal disease develop.

ACUTE COLONIC PSEUDO-OBSTRUCTION

Since originally being described by Sir Heheage Ogilvie in 1948[76] this syndrome has carried a variety of names such as false colonic obstruction, paralytic ileus of the colon, adynamic ileus of the colon, spastic colonic ileus, functional obstruction of the colon,[2] as well as the most common, Ogilvie's syndrome. As the myriad of terms imply, the syndrome is defined as acute dilatation of the colon, predominantly the cecum and ascending colon, without luminal obstruction. The syndrome may mimic a mechanical obstruction.

The syndrome is usually seen in the setting of severe underlying disease or during the postoperative period, making it of obvious concern in the intensive care setting. An extensive review of the associated conditions is beyond the scope of this article but has been compiled in other publications.[2, 73, 101, 112, 115] Associated medical conditions include sepsis, myocardial infarction, congestive heart failure, respiratory failure, renal failure, pancreatitis, decompensated cirrhosis, and a variety of neurologic disease states such as Parkinson's disease, cerebrovascular accidents, multiple sclerosis, and meningitis. Toxic metabolic abnormalities have been associated, including hyponatremia, hypokalemia, alcoholism, and lead intoxication. Medications implicated include analgesics, anticholinergics, and psychotropics. Associated surgical procedures include craniotomy; urologic procedures, including prostatectomy and renal transplant; obstetric and gynecologic procedures, such as cesarean section and normal vaginal delivery; orthopedic surgery such as hip replacement; and cardiothoracic surgery, such as coronary artery bypass grafting. In addition, the syndrome has been described in the setting of major trauma and burns. Despite these associations, a significant minority of cases (5%–12%)[73, 112] are considered idiopathic.

This array of associated conditions has done little to further our understanding of the syndrome's pathogenesis. Ogilvie first proposed that the disorder was the result of sympathetic neurologic inhibition because his two cases involved celiac plexus invasion by intra-abdominal malignancy. This would result in unopposed parasympathetic activity and distal regional spasm. A more recent hypothesis[101] involves disordered parasympathetic activity, especially the parasympathetic innervation effecting the colon distal to the splenic flexure from the sacral plexus (S_2–S_4). Because pseudo-obstruction is common after pelvic insults (obstetric/gynecologic or genitourinary surgery), it is possible that there is a secondary inhibition of distal parasympathetic stimulatory innervation leading to a functional obstruction. In any event there appears to be some form of imbalance between these two systems that has yet to be fully elucidated. In addition, the roles of the enteric nervous system and circulating substances such as prostaglandins and gastrointestinal hormones have yet to be fully clarified. The pathogenesis will likely be multifactorial. Perhaps the wide variety of associated conditions speaks for multiple causes that lead to a single common outcome—colonic pseudo-obstruction.

Clinically, as previously stated, these patients present much like patients with mechanical colonic obstruction. Symptoms can include nausea, vomiting, abdominal pain, and swelling, which gradually develop over 3 to 4 days. The patient generally stops passing flatus and stool, although diarrhea can occur. Physical examination generally reveals a distended abdomen with diffuse tenderness and bowel sounds, which can be hyperactive, hypoactive, or absent. The clinical picture can obviously change should perforation occur, leading to high fever, peritoneal signs, and leukocytosis. Note, however, that fever and leukocytosis can occur without perforation, albeit less frequently (in Vanek's series,[112] fever, 31% versus 78%; and leukocytosis, 27% versus 100% in nonperforated versus perforated cases).

An abdominal roentgenogram with both supine and upright views is an obvious requirement. An abrupt cut off of colonic air can occur anywhere in the colon but is usually in the splenic flexure (56%),[112] making air in the descending and rectosigmoid colons less common. Air fluid levels can be present (42%).[112] The cecum is the portion of the colon that becomes most markedly dilated and is the site of perforation. Cecal diameter can be easily followed in serial abdominal roentgenograms and has implications on management (see later discussion). The diagnostic use of contrast roentgenograms is controversial. Their role is obviously to rule out a mechanical obstructing lesion, but some authors fear cecal perforation as a result of the procedure,[2] whereas others advocate their use,[101] especially using Gastrograffin. In some instances they can be therapeutic, and the reported morbidity is 1%.[112]

Central to the management of patients with pseudo-obstruction is an understanding of its primary complication, cecal perforation. Cecal perforation is a well-recognized complication of large bowel mechanical obstruction, occurring in 1.5% to 7% of cases.[103] According to LaPlace's Law, the cecum with its large diameter requires only small increases in intraluminal pressure to markedly increase wall tension. Progressive dilation leads to longitudinal splitting of the taenia, followed by splitting of the serosa and mucosa. This is further complicated by mucosal ischemia, which also occurs with colonic dilatation, especially on the antimesenteric border of the colon.[103] The actual diameter at which cecal perforation occurs is difficult to predict. Indeed, patients with chronic constipation can have thickened, flaccid bowel walls resistant to perforation at large diameters.[103] It is generally accepted, however, that a normal cecal diameter is less than 9 cm and that a diameter of 9 to 12 cm should raise concern of possible perforation. Increases beyond 12 cm can greatly increase risk of perforation. Overall risk of cecal perforation is estimated at 3% to 14.8% of cases.[53, 73] In one series[112] 7% of patients with diameters of 12 to 14 cm perforated or had severe ischemia, whereas 23% did so with diameters more than 14 cm. The importance of this is obviously in overall outcome. Patients with perforation or ischemia have a mortality of 36% to 44%

compared with 15% in those without these complications.[112] Obviously these patients with concomitant medical and surgical problems cannot afford further physiologic compromise.

The management of these patients can include conservative medical therapy, colonoscopy with decompression, or surgical decompression, and is dictated by the patient's overall clinical condition and risk of perforation. Most authors believe that patients with a cecal diameter less than 12 cm and without signs of perforation and ischemia should first be treated with 48 to 72 hours of conservative medical management.[2, 112] This should include allowing nothing by mouth; placement of a nasogastric tube to suction; correction of any electrolyte abnormalities; discontinuation of any medications that effect gastrointestinal motility (if possible), including narcotics, anticholinergics, psychotropics; placement of a rectal tube; and attention to therapy of the underlying disorder. Of course, close clinical evaluation is necessary, including repeated physical examination and serial abdominal radiographs to evaluate cecal diameter. Simple medical management can be successful in up to 32%[74] of patients.

The widespread use of colonoscopy in recent years has been applied to acute pseudo-obstruction. Initial fears regarding the risk of perforation seem not to be warranted in this situation. Kukora and Dent[65] first described successful decompression in five of six patients with colonic pseudo-obstruction. Subsequent reviews[14, 74, 103] have clarified its usefulness but also the high rate of recurrence after simple decompression. Cumulative data[14] indicate that 81% of patients treated with colonoscopy have successful decompression, although 15% reoccur. The technique of colonoscopy in this setting requires the use of little sedation. Extensive preparation of the colon (short of evacuating the descending colon of formed stool) is not necessary. The colonoscope is passed proximally as far as possible and often, reaching the hepatic flexure is sufficient. The lumen is deflated as the colonoscope is withdrawn at 4- to 5-cm intervals. Additional benefits of colonoscopy include the ability to rule out luminal lesions and thus avoid contrast radiographs, and the ability to evaluate the mucosa for viability and therefore identify areas of ischemia earlier. More recent studies[53, 74] have advocated the placement of a decompression tube at the proximal site reached by colonoscopy in an effort to minimize reoccurrences of colonic dilatation. This can be placed by passing the tube attached to a biopsy forceps, as done by Nano et al,[74] or passing the tube placed over a colonoscopically placed guidewire, as done by Harig et al.[53] In the small series by Harig et al, simple decompression with colonoscopy had a reoccurrence rate of 44% and there were no reoccurrences in a group treated with colonoscopy and tube placement.

Although colonoscopy has limitations one must remember that it may provide precious time during which the clinical condition of a severely ill patient could be maximized. To place its use in perspective, there are some authors who do not routinely advocate colonoscopy as initial therapy (i.e., concomitantly with medical therapy). In a small study of 25 patients with a mean cecal diameter of 11.7 cm, Sloyer et al[98] had improvement in 96% of patients in a mean of 3 days without colonoscopic decompression. Although these patients all had malignancy as their underlying diagnosis and therefore may be a select subgroup, it highlights the need for a balanced approach to these patients.

Should cecal perforation occur or continue to be a threat despite aggressive medical and colonoscopic therapy, surgery is appropriate. In case of perforation or ischemia, resection of the involved colon is appropriate. With a viable colon, a tube cecostomy is performed to provide decompression. A recent report described percutaneous cecostomy performed in five patients, four of whom had previously been unsuccessfully treated with endoscopic decompression.[114] All had cecal diameters more than 12 cm. Ponsky and Azsod[83] also described endoscopic cecostomy.

These would certainly be attractive alternatives to surgery in this patient population at high surgical risk.

ACUTE GASTRIC DILATATION

Acute gastric dilatation is a rare disorder characterized by the acute failure of gastric emptying with associated hemodynamic compromise. It should be distinguished from mechanical gastric outlet obstruction, which might be seen in peptic ulcer disease or gastric volvulus. The cause of this syndrome is unknown, but because of its association with a wide variety of medical conditions and postoperative states, knowledge of the syndrome necessary for the intensivist.

Although Rokitansky is credited with first describing acute gastric dilatation in 1842, his description is that of the superior mesenteric artery syndrome. The superior mesenteric artery syndrome[1, 5, 66] is vascular compression of the third portion of the duodenum as it passes between the acute angle formed by the superior mesenteric artery and the abdominal aorta. It is usually associated with rapid weight loss but may occur with immobilization and body casting (hence the term "cast syndrome"). Although this syndrome may occur in debilitated patients in an intensive care setting, it usually does not present with severe dilatation with hemodynamic compromise. Rather, it presents with recurrent episodes of nausea and vomiting and is easily diagnosed with contrast examination.

Numerous conditions are associated with acute gastric dilatation. In an extensive review by Rimer[69] 60% to 70% of cases occurred in patients after surgery. The routine use of postoperative nasogastric suction and sophisticated monitoring of fluids, electrolytes, and acid base balance has made this less common. Associated surgical procedures include most intra-abdominal and pelvic surgery as well as fracture, trauma, and retroperitoneal hemorrhage. Medical conditions include various metabolic diseases (notably diabetes mellitus, disorders of calcium metabolism, uremia, hepatic coma), inflammatory diseases (sepsis, endocarditis, tuberculosis), neurologic disease (multiple sclerosis, autonomic dysfunction, cerebral tumors, acute porphyria), and psychogenic diseases. Drug-induced gastric dilatation is seen with medications that affect gastric motility, such as opiates, psychotropics, and atropine. Rare cases of idiopathic gastric dilatation have also been described.[23]

Clinical features[24] include abdominal pain, nausea, and recurrent vomiting of material that may contain bile pigment. Physical examination is significant for marked abdominal distention, hypoactive bowel sounds, tympany to percussion, particularly in the upper abdomen, and a succession splash, indicating liquid and gas. Plain films of the abdomen reveal massive gastric dilatation often extending into the pelvis with an air-fluid level. The dilatation may have an abrupt cut off in the third portion of the duodenum. Contrast studies are generally not warranted. Early metabolic parameters may indicate a hypochloremic metabolic alkalosis with evidence of dehydration.

The more ominous clinical signs include progressive hypotension, a developing acidosis, and anuria, indicating hemodynamic compromise and shock. The hemodynamics of shock in acute gastric dilatation have been well studied in animal experiments.[37, 79] Catheters placed in the thoracic and abdominal portions of the inferior vena cava during periods of gastric dilatation have revealed a marked increase in abdominal inferior vena caval pressure with associated decreased blood flow. No significant change in flow in the thoracic inferior vena cava or in the superior vena cava was noted. The above changes were associated with a decreased cardiac output and cardiovascular collapse. A functional obstruction of the inferior vena cava and decreased venous return result in decreased cardiac output. In addition, changes in the portal venous system lead to accumulation of fluid within the splanchnic circulation.

Shock can occur in conjunction with another known complication of this syndrome—free gastric perforation.[90] Surprisingly, this invariably occurs along the lesser curvature with disastrous results.

The most effective measure is prevention of utilizing nasogastric intubation in conjunction with close physiologic monitoring. For other patients, a high index of suspicion must be maintained, and passage of a nasogastric intubation, limitation of medications that affect gastrointestinal motility, and correction of electrolyte and acid-base disturbances must be quickly initiated. Perforation must be treated surgically but has a high mortality.

ISCHEMIC BOWEL DISEASE

Ischemic bowel disease is one of the more challenging disease entities encountered in the intensive care unit setting. It occurs in many different clinical situations common in the intensive care unit, including hypoperfusion, embolization, and a wide variety of other clinical conditions. The diagnosis is often difficult and the delay may lead to patient demise before intervention can be instituted.

Anatomy of Mesenteric Circulation

Almost the entire gut is supplied by three main branches of the aorta, namely the celiac axis, the superior mesenteric artery, and the inferior mesenteric artery. Branches of these arteries supply all intraabdominal organs of the gastrointestinal tract from stomach to rectum. These branches also make up the vast collateral supply of the gut represented by the arcades in the small intestine and by the Arc of Riolan and the marginal artery of Drummond in the large intestine. Given the extent of collateral circulation in the gut, all intra-abdominal viscera may adequately be supplied by patency of only one of the three major mesenteric vessels if gradual occlusion of the other two occurs.[87] Despite this tremendous collateral circulation, ischemic insults can occur in several ways.

Ischemic Syndromes

Although chronic ischemic syndromes do exist, they are only pertinent to the intensive care unit because patients with these syndromes are at increased risk of developing acute syndromes. This section focuses on four of the most commonly seen acute ischemic syndromes: (1) acute mesenteric arterial thrombotic occlusion; (2) mesenteric arterial embolization; (3) nonocclusive intestinal infarction; and (4) mesenteric venous thrombosis.

Before beginning with any of these specifically, it is helpful at this point to make a few general comments about the diagnoses of these disorders. Symptoms, signs, and routine labs are generally nonspecific in these entities. Even angiographic demonstration of stenotic narrowing or occlusion does not establish ischemia as the cause of symptoms because vessel caliber correlates poorly with clinical symptoms.[71] In addition, patent vessels do not rule out ischemic disease because the occlusive process may be localized to smaller less well visualized vessels.

Acute Mesenteric Arterial Thrombotic Occlusion. This syndrome is most commonly seen in association with atherosclerosis but may also be seen in patients with dissecting aortic aneurysm and fibromuscular dyplasia. Patients generally present with severe abdominal pain, which is often located periumbilically and is often colicky in nature. Most important is the fact that pain is out of proportion to physical findings. In the first 4 to 8 hours the abdomen may be slightly distended with mildly decreased bowel sounds and mild midabdominal tenderness to palpation.

During the next several hours the examination becomes more impressive with frank distension, tenderness, and rebound. In addition, if several bowel movements occur, blood in the rectum may be found. Tachycardia, fever, and hypotension are frequently present at this point. By 12 to 24 hours the patient has unequivocal peritonitis and blood in the rectum. The prognosis is bleak at this point.

Given the poor specificity of symptoms and signs, it is essential to look for other clues in making this diagnosis. History or physical findings suggesting vascular disease elsewhere in the body are helpful. In patients with recurrent postprandial pain, patients with recent episodes of hypotension or hypoxia, or patients with evidence of arterial embolization, this diagnosis must be strongly considered. The white blood cell count may be elevated and there may be hemoconcentration. The amylase may be elevated, and elevation of serum and peritoneal fluid phosphate concentration has been described.[39] Blood is quite common in the stool or in a nasogastric aspirate. A metabolic acidosis is also rather common, especially late in the course of the disease. There may be radiographic evidence of an ileus, or there may be evidence of a formless loop of small bowel, although this is less common. Computed tomography (CT) and sonogram are only helpful because they can rule out other disease entities in the differential, such as perforated viscus or pancreatitis. The use of angiography must be carefully weighed clinically in terms of risks and benefits. A patient with clear signs of peritonitis should probably not undergo angiography. On the other hand, a patient seen early in the course of an illness where acute mesenteric arterial thrombotic occlusion is being considered may well benefit from an angiogram and catheter placement for infusion therapy.[16] It is essential to emphasize that the key to early diagnosis rests on a strong clinical suspicion in the correct clinical setting and particularly to a disparity between pain and physical findings.

Treatment of acute mesenteric arterial occlusion is largely supportive. Fluid replacement is essential. With sepsis, avoid the use of norepinephrine if possible. Dopamine should be used in its place because it has less effect on intestinal blood flow. Nasogastric suction, electrolyte monitoring, and replacement and early antibiotics after culture are all essential to successful treatment. The use of papaverine or other mesenteric vasodilators through a catheter placed during angiography has clearly decreased mortality in this disease.[18] Finally, surgical intervention is often essential, with resection of necrotic bowel and revascularization of viable bowel through bypass grafts, embolectomy, and endarterectomy. So called second-look procedures are often essential in identifying and resecting any bowel that proves to be nonviable. Use of this aggresive approach to this disorder has improved survival from a mere 10% to 30% to 50% to 55% rate.[16] In addition, this approach has resulted in the ability to preserve more bowel, resulting in fewer postoperative long-term complications such as short bowel syndrome.

Mesenteric Arterial Embolization. Most patients with mesenteric arterial embolization have arteriosclerotic heart disease or valvular heart disease and have mural thrombi. However, other patient groups need to be considered, such as those with bacterial endocarditis, valvular prostheses, atrial myxomas and the large group of elderly patients with atherosclerotic plaques in their aorta. Most emboli lodge in the superior mesenteric artery because of the caliber of this vessel and the obliquity of the take off from the aorta.

The opportunity to make the diagnosis of mesenteric arterial embolization is greater than that for thrombotic arterial occlusion because it occurs very suddenly in an appropriate clinical setting such as atrial fibrillation. Two other clinical clues may be helpful in diagnosis. First, patients often have a history of other embolic events. Second, there may be evidence of simultaneous peripheral embolization. Patients present with the sudden onset of severe midabdominal cramping pain often associated with vomiting and diarrhea. In the early stages there is no bleeding, the abdomen is soft, and bowel sounds are normoactive. As time goes on, however, the clinical picture comes to be identical to that seen with acute mesenteric arterial occlusion described earlier. Preoperative angiography for diagnosis and catheter placement is necessary.

Treatment is supportive and identical to that described earlier for arterial occlusion. Use of papaverine or other vasodilators reduces mortality.[15] Most of the emboli lodge proximally and are thus quite accessible to embolectomy. Often early operative embolectomy is all that is necessary and the entire gut is preserved. Second-look operations are often useful in terms of defining viable versus nonviable areas of gut. Given the opportunity for earlier diagnosis and thus earlier intervention, the prognosis for acute mesenteric arterial embolization is better than that for arterial occlusion.

Nonocclusive Intestinal Infarction. This syndrome is defined by intestinal infarction without demonstration of occlusion of the mesenteric arteries. It generally occurs in younger patients than the groups described earlier in this section and includes those patients with severe congestive heart failure, shock, anoxia or recent myocardial infarction, although a small group seems to have no clear precipitating event. The common use of alpha-adrenergic agents in these settings further decreases mesenteric blood flow.

Patients present in a manner similar to that of acute arterial occlusion. The key to diagnosis is a strong index of suspicion in patients who have abdominal pain. The role of angiography in this entity is well defined. There are several angiographic findings that are relatively specific for nonocclusive intestinal infarction including irregular branching of the superior mesenteric artery, spasm of the arcades, and impaired filling of the intramural vessels.[50] These findings are present in about 50% of cases.[71] Angiography also helps to exclude occlusive disease, thus giving time for resuscitation and stabilization secondary to surgery. Finally, placement of a catheter at angiography allows for use of intra-arterial vasodilators in both nonoperative and preoperative patients.

Treatment of nonocclusive intestinal infarction is again largely supportive. Maintaining cardiac output, oxygenation, and blood pressure without the use of alpha-adrenergic vasoconstrictors is essential. Replacing fluids and electrolytes and treating infections early is also important. Again, the use of intra-arterial vasodilators clearly reduces mortality. The decision of whether to operate on these patients is very difficult. Patients brought to the operating room in severe congestive heart failure or shock have a very high mortality, yet patients with intestinal infarction also have the same high risk. One general recommendation might be that patients with evidence of peritonitis suggesting infarction should be brought to the operating room as soon as the patient's condition permits, for resection of necrotic bowel. In those patients without peritonitis, angiography, papaverine infusion, and supportive measures may be enough to get the patient through the episode without a surgical procedure.[50]

Acute Mesenteric Venous Thrombosis. This syndrome is a rare entity accounting for 5% to 15% of patients with intestinal ischemia. Ninety five percent occur in the superior mesenteric vein. It is associated with disorders predisposing to stasis in the mesenteric bed (Table 1).

Mesenteric venous thrombosis presents as an acute abdominal catastrophe although somewhat less acute than arterial occlusion. Almost all patients present with fever and abdominal pain, although the location, nature, and severity of this pain is quite variable. More than one half have nausea and vomiting. Diarrhea or constipation are present in about 30%. Occult blood in the stool is present about 50% of the time; bloody diarrhea or hematemesis occurs 15% of the time and usually implies bowel infarction. Mesenteric venous thrombosis also has a different,

Table 1. *Disorders Predisposing to Stasis in the Mesenteric Bed*

- Primary (idiopathic) (20%–35%)
- Parasitic
  - *Ascaris lumbricoides*
- Hematologic or hypercoagulable states
  - Sickle cell disease
  - Polycythemia vera
  - Thrombocytosis
  - Antithrombin III deficiency
  - Protein C or S deficiency
  - Carcinomatosis
  - Trousseau's migratory thrombophlebitis
- Low-flow states
- Abdominal trauma
- Iatrogenic abdominal operations
- Infusion of vasopressin into SMA
- Intraabdominal inflammation and sepsis
  - Cholangitis
  - Appendicitis
  - Diverticulitis
  - Inflammatory bowel disease
  - Pelvic or intraabdominal mass
  - Peritonitis
- Local venous congestion/stasis, hepatic cirrhosis
- Congestion of portal venous radicles by tumor

much less acute presentation occurring gradually over weeks, with increasing abdominal pain. Physical examination is nonspecific. Hemoconcentration and elevated white blood cell count are present rarely.

The diagnosis of mesenteric venous thrombosis is rarely made preoperatively.[88] Abdominal radiographs may show dilation of the small intestine with thickening and irregularity of the bowel wall. CT scan or MR imaging may be useful because a thrombus within the superior mesenteric vein may be seen. Angiography may be useful if the diagnosis is suspected. Arterial spasm of the involved wall with no arterial run off or venous drainage is seen. At surgery, persistence of arterial pulsations coupled with extrusion of the thrombus from cut venous surfaces confirms the diagnosis.

Treatment, as in all of these disorders, is largely supportive. Papaverine is still recommended to help relieve the associated intense arterial spasm described earlier.[17] Anticoagulation postoperatively and for a period of several weeks is also recommended except in patients with significant trauma or those with cirrhosis and portal hypertension.[49] Finally, surgery may be necessary, especially in those patients with evidence of bowel necrosis and resection, and second look procedures may be indicated as well. The prognosis for mesenteric venous thrombosis is better than that for arterial disease, with mortality somewhere between 2% and 50%.[60] Ischemic small intestinal disease occurs in the intensive care setting. The acute onset of abdominal pain in the appropriate clinical setting demands immediate diagnostic and therapeutic measures designed to preserve intestinal viability. History and physical examination generally are nonspecific but pain out of proportion to physical examination is useful in many instances. Aggressive supportive care is essential. Use of papaverine or other vasodilators has reduced mortality in all of these disorders. Surgery remains the mainstay of therapy for necrotic bowel, and second-look procedures are often necessary. Outcome has generally been poor in most of these entities. With earlier diagnosis based on a strong clinical suspicion and aggressive intervention, however, the patient does stand a reasonable chance for a successful recovery.

ISCHEMIC HEPATITIS

Ischemic hepatitis, also referred to as shock liver, refers to the effects of acute circulatory failure on the liver.[35] It is a relatively rare entity, with incidence after an episode of shock estimated to be about 0.5%.[13] This low incidence is explained by at least two factors. First, the liver has a dual blood supply, i.e., the portal vein and the hepatic artery, which afford protection against most hemodynamic disturbances.[35] Second, when the liver is faced with a decrease in splanchnic blood flow, it may extract more oxygen from blood, thus maintaining a constant oxygen consumption. Thus, a short episode of decreased cardiac output generally does not cause shock liver. Indeed, several studies[13, 36] have shown that the characteristic histologic feature of ischemic hepatitis, centrilobular necrosis, occurs much more commonly if the duration of shock is more than 24 hours and only rarely if it is less than 24 hours.

Most reports of ischemic hepatitis describe the entity after impairment of cardiac function. It seems clear, however, that the damage in shock liver is not caused by hepatic congestion. Rather it is attributable to a decrease in blood flow to the liver. Thus, left ventricular failure (and not right ventricular failure) secondary to an infarct or arrhythmia is the most common predisposing event.[22, 25] Ischemic hepatitis may be seen with septicemia, hemorrhagic shock, heatstroke, and acute pancreatitis. In at least one study[46] systemic hypotension was recorded in only a minority of patients with ischemic hepatitis.

Clinical manifestations of ischemic hepatitis are rare because of the generally limited extent of the necrosis. Vague symptoms of anorexia and malaise have been reported, although these are clearly universal in any intensive care unit setting. The patient may occasionally become jaundiced[22, 35] and physical examination may reveal tender hepatomegaly.[75] Generally there is a mild to moderate increase in bilirubin and alkaline phosphatase after a pronounced increase in serum aspartate aminotransferase and alanine aminotransferase to levels up to 40 times normal.[35, 75] Remarkably, alanine aminotransferase exceeds aspartate aminotransferase in most series. There is a rise in lactate dehydrogenase as well.[46] Despite this large increase there is little other evidence of liver dysfunction, and liver failure is very rare.[35] The rapid rise is seen within 48 hours of the ischemic episode and there is a return to normal in 5 to 10 days.[46]

Diagnosis is usually made when a patient with an acute episode of hypotension is found to have an abrupt change in the biochemical tests of liver dysfunction. Differential diagnosis includes viral or drug-induced hepatitis. Hepatitis A and B may be excluded by serologic testing with relatively good sensitivity. Present assays for hepatitis C cannot be utilized acutely. Drug-related hepatitis is often suggested by history. Patients in the intensive care unit are usually on multiple drugs and idiosyncratic reactions cannot be excluded. Finally, patients with ischemic hepatitis improve after the shock episode much more rapidly than would be expected with viral hepatitis.[22] Liver biopsy is usually not necessary but the finding of centrilobular necrosis is distinct from the histologic changes seen with viral or drug-induced hepatitis.

Treatment of ischemic hepatitis is based on the treatment of the patient's underlying illness. Indeed, the prognosis is primarily determined by the conditions that induced hypotension.[13] When patients recover from their episode of shock the hepatitis resolves in 5 to 10 days. In itself ischemic hepatitis can be considered generally benign and self limiting.[35] However, patients with underlying liver disease of any cause seem to have a more severe course when ischemic hepatitis develops. Indeed, patients with chronic liver disease who develop acute circulatory disorders have been reported to more often develop fulminant hepatic necrosis and failure. Of interest is one report of diffuse hepatic calcification after an episode of cardiogenic shock.[94]

In summary, ischemic hepatitis is marked by a pronounced rise in the biochemical tests of liver dysfunction in the face of an acute circulatory disturbance of almost any cause, although most commonly cardiac. The diagnosis is usually evident but viral and drug-induced hepatitis must be ruled out. Prognosis is generally determined by the patients underlying illness and those who do well have full resolution of their hepatitis; the only exception to this being those with significant underlying liver disease.

PANCREATITIS IN THE INTENSIVE CARE UNIT

Pancreatitis is both a common cause of admission as well as a common occurence in the intensive care unit. While in the United States alcohol is easily the most common cause of pancreatitis, there are many medications, surgical and medical procedures, and unknown factors that result in clinical pancreatitis (Table 2). Many of these procedures result in intensive care unit admissions and many patients are treated with medications that cause pancreatitis (Table 3). This section does not focus on the diagnosis, management, or prognosis of pancreatitis; reviews of this may be found in various texts and review articles.[27, 99, 100, 102, 111] Rather, we focus on the various situations that engender pancreatitis in the intensive care unit.

Few data are available about the precise incidence of pancreatitis in the intensive care unit. However, Kameya et al[62] studied 53 consecutive patients admitted to an intensive care unit and found that 27 (51%) patients had hyperamylasemia. Evaluation of these patients revealed that only 4 of the 27 actually had

Table 2. *Conditions Associated with Acute Pancreatitis*

ACCOUNTING FOR >90% OF CASES	ACCOUNTING FOR <10% OF CASES
Ethanol Abuse	Abdominal operations
Cholelithiasis	ERCP—injection into pancreatic duct
Idiopathic	Hyperlipemia
	Trauma
	Hypercalcemia
	Pregnancy
	Peptic ulcer
	Outflow obstruction
	Organ transplant
	Pancreas divisum
	Endstage renal failure
	Cardiac surgery
	Hereditary (familial pancreatitis)
	Scorpion bite
	Miscellaneous
	Hypoperfusion
	Viral infections
	Mycoplasma pneumoniae infection
	Intraductal parasites

Modified from Soergel KH: Acute pancreatitis. *In* Sleisinger MH, Fordtran JS (eds): Gastrointestinal Disease, ed 4. Philadelphia, W. B. Saunders Company, 1989.

Table 3. *Drug-Induced Pancreatitis*

DEFINITE ASSOCIATION	PROBABLE ASSOCIATION
Ethyl alcohol	Chlorthalidone
Methyl alcohol	Ethacynic acid
Organophosphorous insecticides	Phenformin
6-mercaptopurine	Nonsteroidal antiinflammatory agents
(Hydro)chlorothiazide	Nitrofurantoin
Furosemide	Methyldopa
Sulfonamides	Corticosteroids
Tetracycline	Iatrogenichypercalcemia
Pentamidine	
Estrogens	
Intravenous lipid infusions	
Valproic acid	
L-Asparaginase	
Azathioprine	
Dideoxyinosine	
Zidovudine (AZT)	

Modified from Soergel KH: Acute pancreatitis. *In* Sleisinger MH, Fordtran JS (eds): Gastrointestinal Disease, ed 4. Philadelphia, W. B. Saunders Company, 1989.

pancreatitis. Other common causes for the rise in amylase were the postoperative state, respiratory disease, heart disease, and renal failure. Clearly, when hyperamylasemia is noted in an intensive care unit patient, other diagnostic considerations besides pancreatitis need be considered. In patients in whom true pancreatic inflammation is present, the following situations should be considered.

Medications

Thiazide diuretics are well established as a cause of pancreatitis. The incidence is related to dose and duration of therapy, and attacks are often severe. Furosemide is a rare cause of pancreatitis but has been reported in dosages as low as 40 to 100 mg/d.[59] In terms of antibiotics, sulfonamides and tetracycline have been definitely implicated, and nitrofurantoin has a probable association. Intravenous lipid infusion is quite common in the intensive care unit and may be associated with pancreatitis. Iatrogenic hypercalcemia such as that from total parenteral nutrition has also been causative. Azathioprine, commonly used after transplantation is associated with pancreatitis. Steroids used in the intensive care unit for various disorders have a probable association and, at least according to Reimenschneider, this association is dose related,[86] although this last point remains controversial. Medications used for patients with human immunodeficiency virus (HIV) disease, including pentamidine, Zidovudine and dideoxyinosine, also produce acute pancreatitis.

Abdominal Operations

The incidence of pancreatitis after gastrectomy and biliary tract surgery is between 0.2% and 0.8%.[99] Because of the almost universal occurrence of abdominal pain after surgery and the high incidence of elevated serum amylase in this setting, the diagnosis of pancreatitis is often difficult. The mortality of postoperative pancreatitis has been reported to be between 25% and 50%.[99] However, in 1988 Thompson et al[109] reported on 52 patients who developed acute pancreatitis postoperatively over a 9-year period. In their series, the most common operations preceding pancreatitis were biliary tract procedures,[109] intestinal resection,[86] and colectomy,[86] with a mortality rate of 17%, whereas 31% experienced complications including pseudocysts, abscesses, or fistulas. They found that type of surgery, age of patient, and frequency of hypotension or renal failure had no association with development of complications.

Trauma

Obviously the pancreas may be injured from both penetrating and blunt trauma, and this represents the most common cause of injury in children. With penetrating injuries, the prognosis is determined by the amount of tissue damage. With blunt trauma, pancreatic ducts may be disrupted, with subsequent pseudocyst and fistula formation. Because pancreatic trauma may coexist with damage to the small intestine, serum amylase is an unreliable marker for pancreatitis in this situation.

Renal Transplant

Several studies since the early 1970s have discussed the development of acute pancreatitis after renal transplant. The incidence ranges from less than 1% to 7%, developing from 1 week to 7.5 years after transplant. Although in most instances the exact cause was unclear, many causes have been described, including direct injury during surgery, hypercalcemia, cytomegalovirus infection, use of azathioprine and steroids, and coexistent gallstones.[28, 38] The mortality from pancreatitis after renal transplant has been reported to be as high as 53%.

Cardiac Surgery

Pancreatitis is a fairly common gastrointestinal complication after all kinds of cardiac surgery,[64] with an incidence reported as less than 1% to 2.7%. In 1989, Rattner et al[85] reported the incidence of hyperamylasemia after cardiac surgery to be as high as 32%. In this study, 56 of 300 patients had isolated hyperamylasemia, 32 of 300 had subclinical pancreatitis with mild symptoms and quick resolution, and 8 of 300 had overt pancreatitis. Interestingly, regardless of cause of elevated amylase, mortality for this group was higher (7.5%) than mortality for those without elevated amylase (0.9%) even when the elevated amylase was not of pancreatic origin. The precise cause of pancreatitis after cardiac surgery remains unclear. Several factors have been implicated with cardiac transplant. Immunosuppresive therapy alone and with subsequent development of infectious causes such as cytomegalovirus have been invoked. Rejection may play some role because there may be common antigenic determinants between host tissue and transplanted tissue, with the subsequent development of autoantibodies. Low-flow states, which are quite common after cardiac surgery, may cause ischemic injury to the pancreas, thus causing pancreatitis.[3, 51] Indeed, Warshaw and O'Hara[116] showed that major pancreatic injury occurred in 9% of patients who died of oligemic shock. Pancreatitis is commonly misdiagnosed on the basis of an elevated amylase after extracorporeal perfusion when hydoxyethyl starch is used for volume expansion or pump priming. This compound binds serum amylase, forming a macroaggregate that is slowly cleared.[26]

SUMMARY

Various causes of acute pancreatitis are commonly encountered in the intensive care unit. Some of these factors such as trauma, transplantation, and various cardiac and noncardiac surgery bring patients to the intensive care unit. In other patients, the pancreatitis develops subsequently. A high degree of suspicion is indicated, but not all hyperamylasemia is pancreatitis.

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Trauma Anesthesia and Critical Care

Anesthesiology's Oldest Subspecialty Reborn

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HISTORY AND PHILOSOPHY

The title of this article stems from the ancient relationship between trauma, the injured patient, and the practice of anesthesiology, which is basically the relief of pain and the acute preservation of life and limb. In fact, even before the formal study of human anatomy was undertaken and the sophistication to explore the body's cavities by way of scalpel existed, the relief of pain due to trauma was being attempted with both pharmacologic and nonpharmacologic means.[72] Archaic references[60] detail such activity on the battlefields of classical Greece.

A review of the development of anesthesiology through the millennia reveals that, almost without exception, the driving force behind advancements in the profession was the search for improved methods of managing pain—either that caused directly by injury or indirectly by its treatment. With the maturation of basic scientific and clinical aspects of medicine, for the most part since the middle of the nineteenth century, the practice of anesthesia was used to support and facilitate other developing areas of medicine and surgery (e.g., cardiothoracic, neurologic, gynecologic surgery). However, interest in the care of the injured was retained, albeit at various levels. This interest accelerated slightly during World War I through to World War II.[12, 85] But it was not until the mid-1980s that the attention of anesthesiologists was once again focused on their role in the peri-

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operative management of trauma.[53] With the development of "trauma anesthesia and critical care" as a specialized area of practice,[54] anesthesiology's newest subspecialty is ironically its oldest.

Analysis of the population of trauma patients and their particular needs revealed the need for an anesthesia care provider specializing in trauma.[97] The trauma anesthesia/critical care specialist (TA/CCS) has evolved to meet these needs.

The breadth and depth of trauma anesthesia and critical care are extensive, perhaps more so than any of its allied specialties (e.g., cardiac anesthesia, obstetric anesthesia). Its practice requires the anesthesiologist to be a jack-of-all-trades and the master of some.

Because the incidence of trauma is projected to mount and because emergency medical treatment is improving dramatically, the number of trauma patients reaching hospitals will continue to increase. Thus, trauma management will become an increasingly large part of the anesthesiologist's practice. This variation in the proportion of practice devoted to trauma patients was predicted more than 10 years ago.[44]

Because trauma does not discriminate, a wide range of patients and injury types are encountered, such as cardiac, neurologic, obstetric, and pediatric. Also, the numbers of elective follow-up procedures and ambulatory care patients are increasing. Both general and regional anesthesia as well as various postoperative pain management techniques are employed for these patients. Trauma anesthesia and critical care is unique for this reason and because it permits the practitioner to be both a leader and a team player. The anesthesiologist may assume primary responsibility for a patient from the time of injury; in many countries of the world, this may begin directly in the field (discussed later), whether at a civilian mass casualty/disaster site, on the battlefield, or at the scene of urban violence.[33, 48] The TA/CCS then continues to provide care through the operative phase, culminating in postoperative critical care. To the best of our knowledge, no other medical specialists possess the proper combination of training and experience permitting them to render such optimal prehospital and intrahospital continuity of care.

The space constraints of this article do not permit us to take the reader on the entire fascinating journey through trauma anesthesia and critical care. The field is so extensive that two full-scale texts have been published recently.[22, 96] However, we do extract salient interesting features of the practice. A special effort has been made to cover germane clinical issues but not in a "cookbook" fashion. Our aversion to doing the latter is borne from our perception that trauma anesthesia and critical care transcends the mundane. True mastery of its practice is achieved by obtaining a profound conceptual grasp of the basic tenets that apply to all aspects of anesthesiology, as well as of the special aspects of trauma and emergency care, and being subject to an array of zany experiences in an exotic variety of locations, all of which culminate in an existential ability to handle any injury with any equipment at any locale.

EPIDEMIOLOGY

Trauma is a significant cause of morbidity and mortality worldwide. Of the 11 million deaths each year in the developed world, 0.8 million (7.3% of the total) are the result of trauma,[109] ranking it as the fifth most common cause of death after ischemic heart disease, cancer, stroke, and respiratory disease. Approximately 350 patients per million per year require intensive care for trauma.[2] The United States is often nefariously regarded (e.g., through the international media) as a country in which an extremely high level of trauma occurs; however, it ranks thirteenth in the developed world, with an annual fatality rate from all causes of trauma of 61.6 per

100,000 population (Table 1). In the United States, injury is the leading cause of death up to the age of 44 years[28] and results in more years of potential life lost than any other disease.[70] Annually, injuries cause between 3.5 and 4 million years of potential life lost, more than that caused by cancer and heart disease combined.[23] The subsequent loss of productivity and medical costs represent a substantial financial burden on society. The National Safety Council estimated the total cost of accidents (excluding suicides and homicides) in 1989 to have been $148.5 billion.[79]

Motor vehicle accidents are the primary cause of trauma deaths within the United States and in many other countries. In the United States, motor vehicle accidents account for a third of all trauma fatalities and are followed in frequency by suicide and homicide (Fig. 1). The appalling number of homicides (20,812 in 1987) in the United States in comparison with that in the rest of the developed world implies a relatively high incidence of penetrating trauma. According to data from the World Health Organization,[109] the only country in the developed world within which this homicide rate is approached is the Soviet Union (17,018 homicides in 1987).

The relevance of these facts to the practice of anesthesiology relates to their

Table 1. *Annual Trauma Fatalities in the Developed World per 100,000 Population**

RANK	COUNTRY	DEATHS
1	Hungary	115.83
2	USSR	88.11
3	France	83.91
4	Finland	82.36
5	Denmark	78.93
6	Austria	78.90
7	Switzerland	77.02
8	Belgium	71.35
9	Luxembourg	70.86
10	Norway	63.67
11	Czechoslovakia	62.25
12	Poland	61.97
13	United States	61.60
14	Bulgaria	60.90
15	New Zealand	60.83
16	Sweden	60.10
17	Yugoslavia	58.58
18	Canada	55.44
19	Portugal	54.32
20	West Germany	52.82
21	Australia	49.63
22	Italy	49.21
23	Iceland	46.80
24	Greece	45.73
25	Japan	44.19
26	Israel	43.86
27	Spain	40.71
28	Ireland	39.29
29	United Kingdom	38.12
30	Netherlands	36.49
31	Malta	20.17

*Collated from the most recent data available (1987 or 1988) from the World Health Organization, representing codes E47–E55 in the 9th revision of the International Classification of Diseases (ICD-9). Data from Romania and East Germany not available.

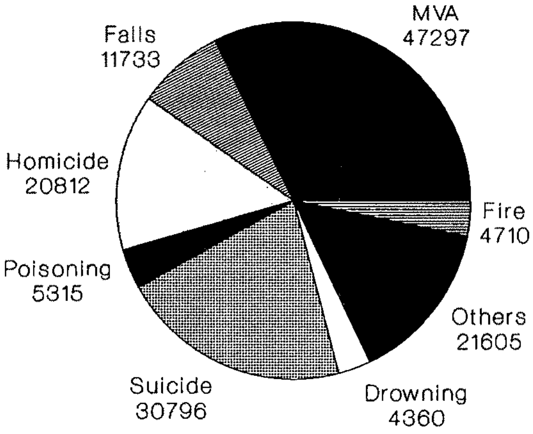

Figure 1. Cause and numbers of trauma fatalities in the United States, 1987.

secondary fallout. One example is the absolute volume and relative number of trauma patients seen in anesthesiology practice as discussed earlier.[49] Another example is that the ultimate morbidity and mortality of this group of patients as well as other long-term sequelae, such as lost wages and increased health care expenditures, are directly related to the quality and intensity of care delivered by appropriately trained medical specialists. These include anesthesiologists who recognize trauma as a specific disease entity, who accept the basic principle that the trauma patient is different from other patients, and who thereby direct their efforts from this perspective.[53] The philosophy of anesthesiologists wholly dedicated to the care of trauma patients (the TA/CCS) is explored in greater detail in the next section.

ORGANIZATION OF TRAUMA CARE

Trauma Systems

Several studies have demonstrated that outcomes are improved when patients sustaining major trauma are taken to regionalized trauma centers rather than to the nearest local hospital. Most notably, in California, two systems of trauma care were compared in adjacent counties.[106] Mortality was higher in the county in which trauma patients were taken to the nearest emergency department than in the adjacent county, where all the severely injured were taken to a single hospital that was structured as a trauma center. At the latter hospital, only 1% of deaths were considered to have been preventable, whereas in the other county, between 28% and 73% of deaths were considered preventable. This county subsequently established a trauma center, and a follow-up study demonstrated a marked fall in the preventable death rate.[20]

Within the United States, regional systems for trauma care have been developed to provide state-of-the-art treatment in a timely manner to all patients at risk of dying from injury. At the hub of a regional trauma system is the Level 1 trauma center, which has specialized facilities and personnel available 24 hours a day (Table 2). Trauma fatalities occur in a trimodal distribution (Fig. 2).[101] Immediate deaths are due to brain or heart laceration and are not amenable to medical therapy. The second peak of deaths occurs within 1 to 2 hours of injury, usually due to severe head injury, hemopneumothorax, lacerations of the spleen or liver or both, or other multiple injuries associated with major blood loss. Patients with these injuries

Table 2. *Trauma Center Organization*

	LEVEL I	LEVEL II	LEVEL III
Philosophy	Identical commitment to excellent care of severe injuries Trauma quality-assurance process Trauma training programs Trauma public edication		Best community commitment to stabilization and transport of severe injuries
	Teaching program Research		
	600–1000 cases/yr		
Facilities	Lighted heliport	Lighted heliport	
Emergency room	24 h/day with trauma-experienced staffing	24 h/day with trauma-experienced staffing	24 h/day with trauma-experienced staffing
Operating room	Staffed and available for trauma 24 h/day	Staffed and available for trauma 24 h/day	Desirable to be staffed and available 24 h/day
Anesthesia personnel	Anesthesiologist with trauma experience 24 h/d	Nurse anesthetist/ anesthesiologist experienced with trauma 24 h/d	In-house anesthesia coverage 24 h/day
Surgery personnel	24 h/day general surgeon and neurosurgeon experienced in trauma; consultants rapidly available	24 h/day general surgeon and neurosurgeon experienced in trauma; consultants rapidly available	Promptly available general surgeon; 24 h/day neurosurgeon availability highly desirable
Surgery case load	At least 50 severely injured patients per trauma general surgeon per year	At least 50 severely injured patients per trauma general surgeon per year	

From Grande CM, Nolan JP, Bernhard WN: Trauma anesthesia in America: 1990. A description of an American trauma centre. Care of the Critically Ill 6:171, 1990; with permission.

benefit most from regionalized trauma care. As trauma center personnel have improved the efficacy of their resuscitative efforts, the third peak (late trauma deaths) has assumed more importance. These late deaths, which are secondary to sepsis and multiple organ failure, occur days or weeks after injury. The sophisticated critical care services provided at a Level 1 trauma center benefit those patients at risk of being part of the third peak. Patients with life-threatening injuries represent just over 5% of the total number of patients requiring hospitalization after injury, which equates to approximately 200,000 cases in the United States each year.[26]

The prehospital care phase is a vital component in the overall trauma system. Emergency treatment in the field (e.g., airway management, intravenous lines, spine immobilization, and fracture immobilization) influences the patient's final outcome. A particularly important and often difficult aspect of prehospital care is to identify the patients who are most severely injured and therefore require triage to a Level 1 trauma center. It has been suggested that an overtriage rate of 100% may be necessary if all patients with severe life-threatening injuries are to be captured.[26]

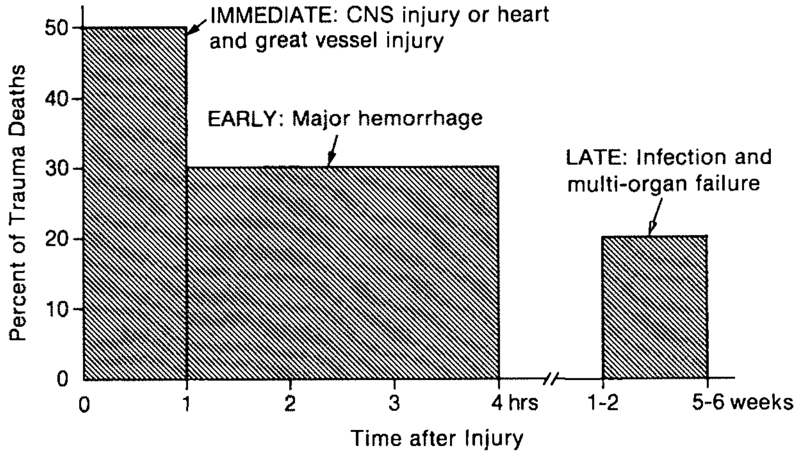

Figure 2. The trimodal distribution of traumatic disease. (*From* Brown DL: Trauma management: The anesthesiologist's role. Int Anesthesiol Clin 25:1, 1987; with permission.)

This implies that 10% of injured patients need to be admitted to the trauma center to avoid missing the 5% that actually have severe injuries. The American College of Surgeons has published guidelines to aid in triage decisions (Fig. 3). The triage decision-making process should include on-line advice and guidance from an experienced physician and must take into account the available resources as well as time and distance factors.[52]

After the decision is made to transfer the patient directly to a Level 1 trauma center, the transfer must be done expeditiously. Transport can be by land ambulance or by helicopter, both of which are associated with advantages and disadvantages.

Other countries with less-sophisticated services for trauma care have watched the development of trauma systems in the United States with great interest. After analyzing a number of studies,[4, 93] a working party commissioned by the Royal College of Surgeons of England concluded that there were serious deficiencies in the management of severely injured patients in the United Kingdom.[83] Several recommendations were made, the most significant being that based on the American experience, trauma centers should be established at the regional level. Unfortunately, economic and political constraints in the United States have placed major stressors on trauma systems[42]; because of these impediments and other factors, only 25% of the United States' population is currently covered by trauma systems.[102] Despite these obstacles, it has been argued in the United Kingdom that although the cost of implementing trauma systems would initially be high, it would eventually be far outweighed by the potential savings associated with a reduction in the fatality rate.[8] Other countries (e.g., Japan, Australia) are also developing large-scale trauma systems despite these potential problems. Other countries, most notably France and Germany, successfully implemented national trauma systems many years ago that function superbly.

Trauma Centers

The criteria for the designation of trauma centers were established by the American College of Surgeons Committee on Trauma and were most recently revised in 1986 (Table 2).[2] Unfortunately, some trauma centers are state- or self-designated, and their standards may not meet the rigorous criteria of the American College of Surgeons.[26] In addition to the features listed in Table 2, the Level 1

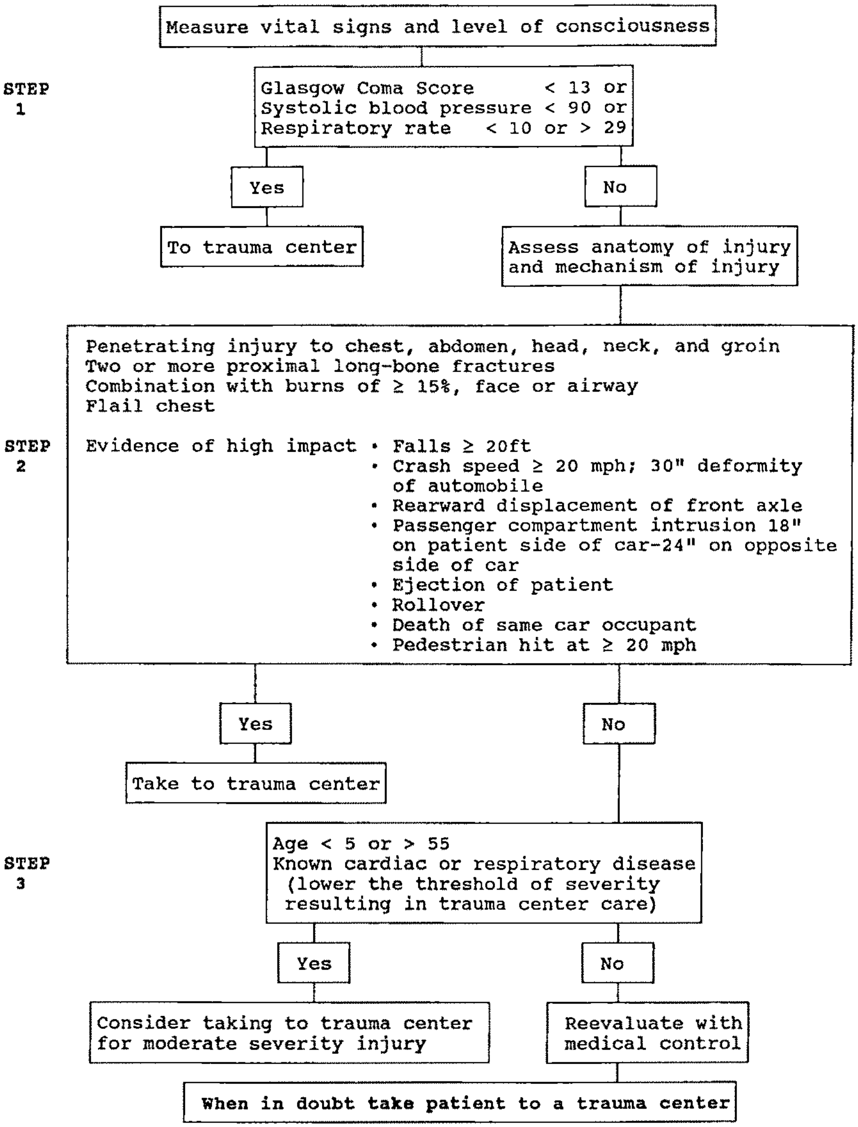
Measure vital signs and level of consciousness
STEP 1
Glasgow Coma Score < 13 or
Systolic blood pressure < 90 or
Respiratory rate < 10 or > 29
Yes
No
To trauma center
Assess anatomy of injury and mechanism of injury
Penetrating injury to chest, abdomen, head, neck, and groin
Two or more proximal long-bone fractures
Combination with burns of ≥ 15%, face or airway
Flail chest
STEP 2
Evidence of high impact
• Falls ≥ 20ft
• Crash speed ≥ 20 mph; 30" deformity of automobile
• Rearward displacement of front axle
• Passenger compartment intrusion 18" on patient side of car-24" on opposite side of car
• Ejection of patient
• Rollover
• Death of same car occupant
• Pedestrian hit at ≥ 20 mph
Yes
No
Take to trauma center
STEP 3
Age < 5 or > 55
Known cardiac or respiratory disease (lower the threshold of severity resulting in trauma center care)
Yes
No
Consider taking to trauma center for moderate severity injury
Reevaluate with medical control
When in doubt take patient to a trauma center

Figure 3. The American College of Surgeons' triage decision scheme.

center should have extensive blood banking facilities and immediate access to a CT scanner and angiography suite. A reliable communications system is essential, permitting exchange of information between emergency care providers in the field and trauma center staff. Before the arrival of a trauma patient, the trauma team is alerted by intrahospital beepers. The composition of this team varies from one center to another[51, 52]; a typical example is shown in Table 3.

Trauma bays in the admitting area should be equipped so that procedures, such as emergency thoracotomy or laparotomy and advanced airway management, can be performed without delay. High-volume intravenous fluid administration sets ("trauma sets") should be primed, and drugs such as induction agents and muscle

Table 3. *Configuration of a Typical Trauma Team*

1 Trauma surgeon attending	1–2 Trauma nurses
1 Trauma fellow	1 Trauma technician
2–3 Trauma residents	1 Blood bank technician
1 Anesthesiologist	1 Radiographic technician

relaxants should be immediately available. One of the admitting area bays at the Shock Trauma Center of the Maryland Institute for Emergency Medical Services Systems (MIEMSS) is shown in Figure 4.

Severely injured patients place a heavy demand on critical care services. Ideally, they should be cared for in designated trauma intensive care units. Care of trauma patients, particularly those with head injuries, must include rehabilitation; thus, the trauma center must also have access to extensive rehabilitation facilities.

The Trauma Anesthesiologist

Over the past three decades, trauma has been clearly identified as a disease. Subsequently, the specialty of dedicated trauma care (traumatology) has developed. Within this specialty, the TA/CCS has emerged as a professional with training and interests that spread across the spectrum of anesthesia, intensive care, and emergency medicine and whose major treatment efforts are focused on the care of trauma victims.[54]

The precise role of the anesthesiologist in the care of trauma patients varies from one facility to another, especially when considered from an international perspective (Table 4).[7, 33, 52, 80] The anesthesiologist should, at a minimum, be part of the trauma team and be present when the severely traumatized patients is admitted

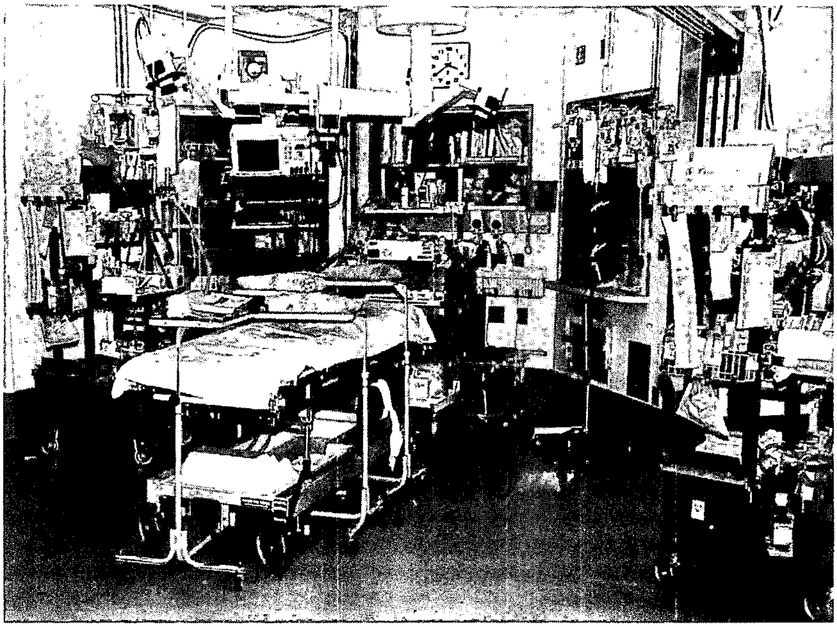

Figure 4. An admitting area bay, fully equipped with monitors, ventilator, full range of drugs for anesthesia, primed drip sets, surgical procedure packs, and high-quality overhead lights.

Table 4. *Potential Roles of the Anesthesiologist in the Care of a Trauma Patient*

Trauma team member	Pain relief physician
Trauma team leader	Prehospital care physician
Anesthesiologist	Critical care transport physician or director
Critical care physician	Disaster planning consultant

From Grande CM, Nolan JP, Oakley PA: Trauma anesthesia: The relationship of the anesthesiology department to trauma systems. *In* Champion HR (ed): Trauma Systems. Cambridge, Cambridge University Press, 1991, in press.

to the hospital, having been appraised extensively of the patient's mechanism of injury and physiologic status before arrival at the trauma center (if he or she has not traveled with the patient from the scene of the accident). The TA/CCS should take part in designing and implementing resuscitation protocols and thereby optimize the initial management of the patient's airway, fluids, and analgesia. In this way, should the patient require immediate transfer to the operating room, the anesthesiologist will not need to waste valuable time becoming familiar with the case.

Postoperatively, trauma patients require effective analgesia. Many patients are candidates for techniques such as epidural infusions, intrapleural catheters, and patient-controlled analgesia. The trauma anesthesiologist has an important role in this acute pain management.

Another important aspect of the anesthesiologist's contribution to the trauma care system is the training of prehospital personnel. Advanced airway management and cannulation skills can be taught conveniently and updated while providing anesthesia for routine surgical cases.[44]

PERIOPERATIVE MANAGEMENT

Assessment and Resuscitation

At admission, many patients with severe trauma are difficult to assess because a history may be unobtainable or because they may be unconscious or obtunded by alcohol or other drugs. Consequently, the traditional management approach of history taking followed by an examination and establishment of a diagnosis before initiating treatment are inappropriate in the management of severe trauma. On the contrary, intricately designed and meticulously orchestrated protocols are effected based on physiologic signs, a knowledge and understanding of the mechanisms of injury, and clinical insight gained from extensive experience.

The priorities of assessment and resuscitation in the trauma patient have been thoroughly defined by the American College of Surgeons in its Advanced Trauma Life Support (ATLS) Program.[1] The use of protocols permits a single coordinated approach to patient care problems, induces uniformity in the training of staff, reduces the incidence of negligence, and facilitates research by establishing a standardized data base.[30] The primary survey (Table 5) and initial resuscitation of vital functions are performed simultaneously, followed by a more detailed secondary survey and, finally, the initiation of definitive care.

An advantage of the trauma team approach is that the anesthesiologist can assess and manage the patient's airway and ventilation while simultaneously assisting the surgeon in the control of any hemorrhage and the initiation of fluid resuscitation.

Baseline blood samples (for assessment of hemoglobin, platelet count, urea and electrolytes, glucose, and coagulation profile) can be drawn from the initial venous cannula, and an arterial sample is sent for blood gas analysis. All victims of major

Table 5. *Primary Survey*

A:	Airway maintenance with C-spine control
B:	Breathing and ventilation
C:	Circulation with hemorrhage control
D:	Disability: Neurologic status (AVPU)*
E:	Exposure: Completely undress the patient

Adapted from American College of Surgeons Committee on Trauma: Advanced Trauma Life Support Course, Instructor Manual. Chicago, American College of Surgeons, 1989. *A = Alert; P = Responds to painful stimuli; V = Responds to vocal stimuli; U = Unresponsive.

blunt trauma should undergo radiography of the chest, pelvis, and cervical spine (which must include the junction of C7/T1). A urinary catheter is passed, and any extremity fractures are splinted. Diagnostic peritoneal lavage or abdominal CT scan should be considered for patients with impaired sensorium (secondary to neurologic injury, alcohol, or drugs) or equivocal abdominal findings (including patients with fractures of the pelvis or lower rib cage). Performing either or both of these procedures before initiating a long operative course is important so that occult intra-abdominal hemorrhage does not cause an untoward change in the planned sequence of events.

Airway Management

Although anesthesiologists have variable roles in trauma patient care, their most vital skill is always airway management.[98] The intact airway must be secured, the threatened airway protected, and an obstructed airway rapidly cleared.

At the very least, all severely traumatized patients require supplementary oxygen. For patients in whom basic airway maneuvers either fail or are inappropriate, some form of advanced airway control is required. The first choice is normally endotracheal intubation via the oral or nasal route. Some general indications for endotracheal intubation in the trauma patient are listed in Table 6.

Oral Versus Nasal Intubation. All patients who have sustained significant blunt trauma should be assumed to have a cervical spine injury until clinically or radiographically cleared. However, in some patients urgent intubation is needed before this can be completed. In these circumstances, considerable debate exists as to the choice of route for intubation: oral or nasal. Underlying the controversy is the fear of producing or exacerbating a neurologic defect in a patient with a cervical spine injury. Fear of cervical spine movement during laryngoscopy has led many anesthesiologists (perhaps incorrectly) to adopt blind nasal intubation as their first choice in acute trauma patients with suspected neck injuries.[46, 47] This method has several disadvantages (Table 7).[50]

At the MIEMSS Shock Trauma Center, the vast majority of acute trauma patients needing urgent intubation are intubated via the oral route in combination

Table 6. *Some Indications for Endotracheal Intubation in the Trauma Patient*

Upper airway obstruction (directly from injury or secondary to a reduced conscious level)
Head injury with GSC* ≤9
Shock
Hypoxemia (chest injury, cervical trauma, etc.)
Requirement for general anesthesia
To aid investigation and diagnosis in the combative patient

*GSC = Glasgow Coma Scale score.

Table 7. *Disadvantages of Nasal Intubation in the Trauma Patient*

Serious risk of inducing epistaxis, especially in the multiple trauma patient who may have coagulopathy
Nasal intubation is not easy in the frightened or combative patient and may result in significant neck movement
Stimulation of the pharynx may induce vomiting and/or raise intracranial pressure
Patient must be spontaneously breathing for reasonable success
Risk of sinusitis in the longer term
Nasal intubation is relatively contraindicated in the presence of a basilar skull fracture because the tube can be pushed into the cranial vault

with in-line cervical immobilization. Before this, a rapid neurologic assessment is made while an attempt to preoxygenate the patient is carried out. The anterior portion of the cervical collar is removed as one person applies cricoid pressure and another performs in-line cervical immobilization. An appropriate dose of an induction agent (usually thiopental) and muscle relaxant (succinylcholine or high-dose vecuronium [or possibly in the near future its newer shorter-acting steroidal analog]) is administered, and laryngoscopy and oral intubation proceed. As noted previously, patients with significant head or chest injuries, may have a critically low PaO_2 even after a period of preoxygenation. These patients will benefit from a "modified rapid sequence induction" technique, whereby positive-pressure mask ventilation is performed after induction of anesthesia and before intubation. Correctly applied cricoid pressure should prevent gastric insufflation during positive-pressure mask ventilation.[69] Anesthesiologists at the MIEMSS Shock Trauma Center have accumulated considerable experience with this technique of orotracheal intubation and have never reported a deterioration of spinal cord function after this maneuver. The most recent data on this subject are summarized in Table 8.

The Difficult Trauma Airway. Unfortunately, in some circumstances, for example, following massive facial trauma, standard methods of intubation are impossible to apply.[21, 57] A task force of the American Society of Anesthesiologists has recently developed an algorithm for managing the difficult airway (Fig. 5). If the trauma patient has an obstructed airway and cannot be intubated, options include surgical cricothyroidotomy, tracheostomy, or needle cricothyroidotomy. In a patient with maxillofacial trauma who has massively disrupted anatomy and associated hemorrhage making mask ventilation impossible,[50] a retrograde technique may be viable if the airway is patent and the patient is cooperative.[13] Major airway

Table 8. *Urgent Intubations in Trauma Patients Admitted to MIEMSS Over a 4-Year Period (1986–1989)**

	NO.	PERCENT OF TRAUMA ADMISSIONS
Trauma admissions	8632	100
Urgent intubations†	1893	21.9
Cervical injuries‡	742	8.6
Urgent intubations with cervical injuries	100	1.2
Emergency cricothyroidotomies§	19	0.2
Documented neurologic deterioration‖	0	0

*Data obtained from the MIEMSS Trauma Registry.[34]
†All intubations within 1 hour of admission.
‡Cervical column and/or cord injuries by radiography or CT or neurologic deficit.
§Within 1 hour of admission.
‖Following intubation.

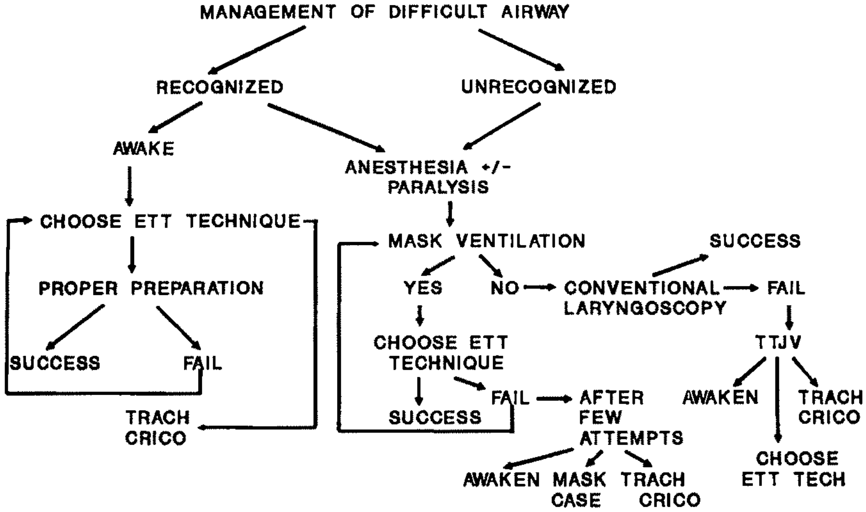

Figure 5. Preliminary ASA Airway Task Force Algorithm. (*From* Benumof JL: Management of the difficult or impossible airway. Annual Refresher Course Lectures, American Society of Anesthesiologists. Las Vegas, 1990, p 163; with permission.)

bleeding effectively rules out a fiberoptic technique. Gentle laryngoscopy with the patient awake may yield a surprisingly good view, because many of these patients will be unable to close their mouths forcibly on a laryngoscope blade. In the awake patient with an acceptable airway but in whom translaryngeal intubation is most likely impossible, an awake tracheostomy may be the method of choice.

In reality, many of these patients, especially victims of gunshot wounds, are decidedly uncooperative. The practical approach in this situation may be to maximize the chance for successful translaryngeal intubation by using one of the rapid sequence inductions[21] followed by direct laryngoscopy. This is done only with the proviso that another confident, experienced, and facile trauma anesthesiologist (or experienced surgeon) is standing by fully prepared for immediate cricothyroidotomy (Fig. 6). Alternatively, needle cricothyroidotomy with jet ventilation can keep the patient alive while a definitive airway is established.[14] Disruption of the larynx with inability to intubate mandates an emergency tracheostomy.[41]

Muscle Relaxants for Intubation. For many years, succinylcholine has been the relaxant of choice for intubating patients with acute trauma because it has the most rapid onset, however, it also is associated with several well-known problems (Table 9). Alternatively, various strategies have been employed to accelerate the onset time of nondepolarizers, including use of the priming,[88] timing,[90] and high-dose techniques.[104] However, none of these strategies can consistently provide adequate intubating conditions as rapidly as succinylcholine.

Several new nondepolarizing relaxants are in clinical development. One of these agents, Org 9426, appears to be particularly promising for use in the patient sustaining acute trauma. Org 9426 is a steroidal analog of vecuronium and shares its property of hemodynamic stability. After administration of an intubating dose of $2\times$ ED_{95}, one group reported adequate intubating conditions at 60 seconds.[108] Clinical duration at this dose level is approximately 35 minutes.

It is important to understand the realistic clinical implications of the "prolonged" recovery times associated with nondepolarizing muscle relaxants (e.g., approximately 70–80 minutes for vecuronium, 0.28 mg/kg). Although these recovery times are

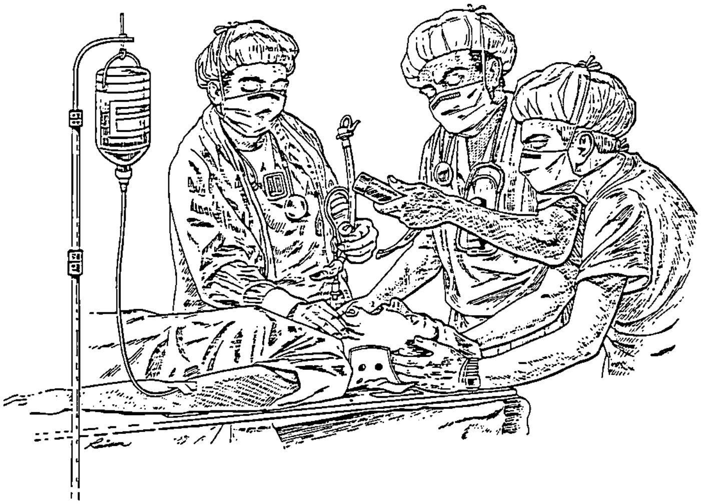

Figure 6. Technique of oral intubation in the emergency trauma patient using laryngoscopy and in-line cervical stabilization. The individual on the left is applying cricoid pressure while holding the endotracheal tube ready. This individual, ideally an anesthesiologist, should be prepared to perform an emergency cricothyroidotomy, having established the landmarks and prepared all the necessary equipment. The assistant on the right is using both hands to maintain the patient's head and neck in a neutral position. The anterior portion of the cervical collar has been removed, and the patient is on a long spine board. (*From* Stene JK: Anesthesia for the critically ill trauma patient. *In* Siegal JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987; with permission.)

extended compared with those associated with a dose of 1.5 mg/kg of succinylcholine (approximately 7–8 minutes), in the severely multitraumatized patient, at least two practical points make these differences redundant. First, in the hectic admitting area of a Level 1 trauma center, even a period of 7 to 8 minutes is considered a long time. In our experience, a trauma team will rarely standby idly and wait for the return of spontaneous breathing in a patient in whom intubation has failed or was difficult. Rather, routine progress through well-established protocols will rapidly lead to an emergency cricothyroidotomy. Second, in view of the extensive peri-

Table 9. *Adverse Side Effects Associated with the Use of Succinylcholine*

Hyperkalemia, particularly after burns, spinal cord injuries, and generalized major trauma. One case report has described a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis.

Increased intraocular pressure; the practical importance of this is highly controversial.

Increased intragastric pressure, although this is counterbalanced by the increase in lower esophageal pressure, thus reducing or eliminating the increased risk of regurgitation.

Increased intracranial pressure, although the clinical significance of this is unknown.

Muscle pains; more likely to affect the patient with minor injuries who ambulates soon after operation.

Prolonged paralysis in patients with atypical pseudocholinesterase.

Cardiac dysrhythmias, particularly bradycardia after repeat doses.

Trigger for malignant hyperthermia.

From Grande CM, Nolan JP: Trauma anesthesia: Airway control in the emergency setting. Journées d'Enseignement Post-Universitaire d'Anesthésie et de Réanimation, in press, 1991; with permission.

operative procedures the seriously traumatized patient will undergo (i.e., diagnostic and therapeutic procedures), even the 70- to 80-minute recovery time required for high-dose vecuronium does not present a management problem.

Initial Volume Resuscitation

Intravascular Access. Patients sustaining trauma associated with major hemorrhage need rapid fluid replacement to restore cardiac output and tissue perfusion. ATLS recommendations are for at least two large-bore (16-gauge or larger) cannulas to be placed peripherally.[1] If this proves impossible, percutaneous subclavian vein catheterization using the Seldinger technique is faster than surgical cutdown and has a similar complication rate.[5]

A valuable approach is to place an 8.5-F sheath into a femoral vein and a 14-gauge cannula into an arm vein, thus, establishing intravenous access above and below the diaphragm. This is important in victims of major trauma because if venous return through either the inferior vena cava or superior vena cava has been disrupted, fluid infused through the defective venous system will be ineffective in filling the heart.

In the hypovolemic patient, cannulation of the femoral vein is more likely to be successful than cannulation through the subclavian or antecubital route.[43] The combination of large-bore, relatively short (3½-inch) sheaths and large-bore (5.7 mm in internal diameter) fluid administration sets (trauma sets) generates the most rapid flow rates.[68]

Warmers and Infusers. Other factors affecting flow rates include the viscosity and driving pressure of the infusate. The addition of saline prewarmed to 45°C to units of packed red blood cells will reduce the viscosity of the blood, thereby increasing flow.[110] Severely injured patients are commonly hypothermic,[71] and the severity of hypothermia correlates closely with survival.[66] As a result of high resistance to flow and inefficient heat transfer, standard fluid warmers are unable to warm blood components to more than 35°C at flow rates exceeding 100 mL/min.[84] A new fluid warmer, the Level 1 (Level 1 Technologies, Inc., Marshfield, MA [Fig. 7]), using a closed-flow single-channel countercurrent heat exchanger and large-bore tubing can heat cold-packed red blood cells to temperatures above 35°C at flow rates of 500 mL/min without red cell damage.[67] Pressure infuser boxes (Alton Dean Medical, Inc., Salt Lake City, UT) connected to a cylinder or pipeline gas supply can be used to increase the infusion rate to 750 mL/min.[91]

The most efficient warming and infusion device currently available is the Rapid Infusion System (Haemonetics Corp., Braintree, MA), which was originally developed for use during liver transplantation.[86] It consists of a roller-pump mechanism and heat exchanger and can deliver blood products at precise rates and under normothermic conditions at a rate as high as 1500 mL/min. Disadvantages of this system are its cost (approximately $52,000 plus $590 for each disposable) and its relative complexity, requiring a set-up time of 5 to 8 minutes and the undivided attention of one person to operate it.

Crystalloids and Colloids. The controversy surrounding the use of a colloid or crystalloid solution for the initial resuscitation from hemorrhagic shock continues and is unlikely to be resolved in the near future.[77] Logic dictates that loss from the intravascular space should be replaced by a colloid solution, because crystalloids will distribute across the entire extracellular space, necessitating replacement volumes of at least three times the blood loss. However, because trauma patient lose interstitial fluid as well as blood, "crystalloid proponents" would argue that this distribution of resuscitation fluid is appropriate.. Recent reviews of the subject conclude that, overall, no good evidence exists documenting a benefit of the use of colloid solutions over crystalloid solutions in the resuscitation of patients in traumatic

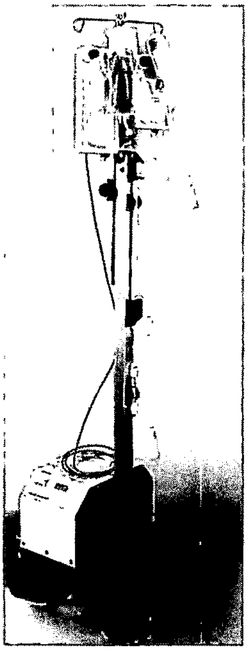

Figure 7. Level 1 Fluid Warmer fitted with 2 Alton Dean pressure infusers. Note the heat exchanger column (*white*), which is an integral part of the three-spike, high-flow, disposable set.

shock.[31, 49, 59, 78] In practice, all available fluids are effective provided the quantities used are adapted to their diffusion space.[36]

CRITICAL CARE TRANSPORT

Movement of the trauma patient from one location to another, an additional facet in the practice of a TA/CCS, is essential for optimal medical management and includes

—Transport from the accident scene
—Interhospital transport if the patient is not initially taken to a Level 1 trauma center or if the patient requires special diagnostic and therapeutic procedures (e.g., hyperbaric oxygen therapy, magnetic resonance imaging) not normally available at many centers
—Intrahospital transport

Aerial Versus Ground Transport

Outside of the hospital, the trauma patient may be transported by land, sea, or air, the last method involving the use of helicopters or fixed-wing aircraft. The vast majority of aerial transports are performed by helicopters, but fixed-wing aircraft are employed for long-range transport. The altitudes such aircraft can attain have important physiologic implications for the trauma patient.

The optimal form of transport from the trauma scene depends on the distance, terrain, time, weather conditions, and the skill levels of the crew when used appropriately. It is likely that helicopters can reduce the mortality and morbidity from severe trauma,[11] however, this is difficult to prove conclusively. In the urban environment, ground transport times to the nearest Level 1 trauma center should be relatively short (less than 15 minutes). A recent study showed no difference between survival rates among trauma victims transported by helicopter and those transported by ambulance in an urban area.[87] In a rural environment, the time elapsing before the helicopter can get to the scene must be taken into account.

Helicopters are likely to be very beneficial in the subsequent interhospital transport of severely injured patients.[16] Disadvantages of using helicopters for critical care transport include the following:

—Cost. Some trauma systems reduce this financial liability by using helicopter time for nonmedical missions. A good example is Maryland's fleet of eight Medevac helicopters, which are owned and operated by the Maryland State Police. Medical missions, constituting 75% of the total missions, take immediate priority over law enforcement duties. Other authorities do not support this type of arrangement and believe that urban air ambulances should be designated for medical purposes only.[26]

—The safety record of hospital-based helicopter programs is appalling; they generate a fatal accident rate five times greater than civilian helicopters in general.[27] Twenty-one hospital helicopter accidents occurred during a period of only 8 months in 1986.[3]

—Helicopter operations are weather dependent.

On the positive side, helicopters have the obvious advantage of speed and, in some instances, accessibility to the trauma patient. Germany has had a well-organized rescue helicopter service since the 1970s. In 1985, it was reported that 25 helicopters with a standard mission radius of 50 km put 90% of the West German population within 15 minutes of medical emergency help.[81]

Physicians in the Field

Although some groups have reported significant benefits from including a physician among the helicopter crew,[10] this also remains a controversial subject. Within the United States, most air ambulances carry only paramedics or flight nurses or both. Conversely, the helicopter systems in Germany and many other countries include physicians, usually anesthesiologists.[103] Many issues must be considered and weighed against each other to arrive at the best alternative for a given trauma system; these include the availability of financial, personnel, and other logistical resources. It seems logical that an appropriately trained physician (e.g., TA/CCS) properly employed within a trauma system could have a significant impact on morbidity and mortality, most directly by maximizing that portion of the "Golden Hour" (the time between the onset of shock and its definitive reversal by appropriate therapy) normally wasted by many factors (e.g., ineffective therapy during field transport). The TA/CCS in the field can provide definitive care to the patient and perhaps "stop the clock" in regards to the Golden Hour.

Physiologic Changes

Aerial Transport. In both helicopters and fixed-wing aircraft, prime mechanical considerations are the cruising altitude and the ability to pressurize the passenger compartment. As altitude increases, both total ambient pressure and the partial pressure of oxygen fall. This gives rise to two considerations: (1) the effects of changes in the size of air spaces in the body (e.g., pleural cavity, bowel, gas emboli) and (2) the effects of hypoxic hypoxia.

At 18,000 feet, atmospheric pressure is half that at sea level. Thus, according to Boyle's law any gas emboli would theoretically double in volume—a serious problem in an injured underwater diver with dysbarism. At 8,000 feet, the partial pressure of atmospheric oxygen has fallen to such a degree that a person with normal respiratory function would have an intra-arterial oxygen tension of only 55 mm Hg.[76] In most fixed-wing aircraft, the passenger compartment can be pressurized, but the cabin pressure is rarely brought to sea-level pressure. High-performance executive jets, frequently used for medical transfers of distances longer than 1000 miles, commonly employ cabin altitudes of 5000 to 8000 feet. Under these conditions, a trauma patient will clearly require supplemental oxygen (Table 10). Helicopters that can fly at very low altitudes can reduce the problems of hypoxia and air space expansion.

Consideration also should be given to the translational forces generated by aircraft maneuvers. For example, a patient with a head injury should be placed with the feet toward the tail of the plane during take off, thus, avoiding increases in intracranial pressure secondary to venous pooling. Other problems associated with aircraft are created by an extremely dry and possibly cold cabin atmosphere. High levels of noise and vibration increase patient anxiety and make even simple tasks, such as auscultating breath sounds and measuring blood pressure, extremely difficult.

Land Transport. The relatively gradual acceleration associated with land ambulances is unlikely to produce significant physiologic changes in the trauma patient, however, sudden deceleration can be problematic.[105] Braking causes venous pooling, and movement of abdominal viscera against the diaphragm could cause further respiratory embarrassment in patients with thoracic trauma or dyspnea. Additionally, the vibration caused by the translational movement of the vehicle also may have detrimental effects.

Intrahospital Transport

Within a trauma center, patients routinely need to be transported from one area of the hospital to another.[35, 55] For example, on admission the trauma patient may necessitate multiple transfers between the following areas: helipad, elevator, resuscitation area, CT suite, operating room, and intensive care unit. Transportation can be extremely hazardous because of the complexity of injuries involved and the difficulty of providing appropriate support en route.[17] The risks of intrahospital transport are probably at least equal to those of ambulance transport but are underestimated.

Safe intrahospital transport depends on an experienced transporting team (anesthesiologist or respiratory therapist, nurse, attendants) and the availability of the necessary equipment. Modern technology has much to offer in terms of small self-contained portable equipment that is ideal for transport. However, even when portable battery-powered electrocardiogram monitors, pulse oximeters, and multichannel pressure monitors are used, the basic essentials, such as stethoscopes and

Table 10. *Oxygen Supplementation Required to Maintain a PaO_2 of 100 mm Hg at Elevations As High As 10,000 Feet*

ELEVATION (FT)					
0	*2000*	*4000*	*6000*	*8000*	*10,000*
21	23	25	27	29	32
30	33	35	38	42	45
40	44	47	51	55	60
50	54	59	64	69	75
60	65	70	76	83	90
70	76	82	90	97	100
80	87	94	100		
90	98	100	Positive pressure required		
100	100				

Adapted from McNeil EL: Airborne Care of the Ill and Injured. New York, Springer-Verlag, 1983, p 121.

the caregiver's natural senses (look, listen, feel), should not be forgotten. Emergency drugs and airway equipment are best carried in a specific lightweight transport resuscitation bag.

Many critically ill patients need a high level of ventilatory support and may deteriorate if simply manually "bagged" during transport. A wide range of portable automatic ventilators are available, many of which include positive end-expiratory pressure or demand valves or both.[18] The most seriously injured patients require complex ventilation patterns that are only possible using advanced critical care ventilators. A ventilator such as the Siemens Servo 900C (Siemens-Elema, Stockholm, Sweden) can be made portable with the addition of oxygen cylinders and a power pack.[55]

Medical Considerations

Although severely ill patients can be transported safely, even at high altitude, several medical conditions require special consideration.[65]

Hemorrhage. The problems of acute anemia are amplified by altitude hypoxia, thus, reinforcing the need for supplemental oxygen.

Thoracic Trauma. In any patient with pneumothorax, the placement of a chest tube capped with a Heimlich valve or McSwain dart should be performed before transport by air.

Eye Injuries. Changes in cabin pressure could lead to the extrusion of global contents in patients with open eye injury.

Maxillofacial Injuries. Patients with maxillofacial injuries often experience surgical emphysema in the soft tissues of the face and neck or partial obstruction of the sinuses by blood and mucus. As altitude diminishes, these pockets of air begin to swell, causing pain, and may threaten the airway if it is not protected by an endotracheal tube.

Orthopedic Injuries. Trauma patients with recently placed plaster casts may have a significant amount of soft tissue swelling, which can result in limb ischemia. All casts should be bivalved if possible. Pneumatic splints are greatly affected by altitude and pressure changes and are therefore contraindicated for aerial transport.

Spinal Injuries. Patients with spinal injuries frequently need to be transported to a neurotrauma unit. If a patient has been placed in a traction system using Gardner-Wells tongs, hanging weights, and a Stryker frame, the system must be modified. The weights may oscillate and overdistract any fracture, and in the event of impact, they become missiles. One alternative is to use a Rambaud cervical traction frame, which substitutes a spring system for the application of traction and is attached directly to the stretcher.

Head Injuries. The physical differences in the aviation transport environment, including a hypoxic atmosphere, pressure-volume changes, and gravitational and centrifugal forces, can adversely affect the patient with a head injury. Adequate ventilation and oxygenation must be ensured by using a low threshold for endotracheal intubation. As is the case with cardiovascular parameters, intracranial pressure also may be monitored during transport.

Burns. Patients with burn injuries can present a multitude of problems during transport, many of which necessitate sophisticated cardiovascular and ventilatory support. In the acute phase, severe hypovolemia and airway problems need to be anticipated.[56]

Anesthesia and Analgesia During Transport

In the United Kingdom, virtually all land ambulances are equipped with Entonox, a mixture of nitrous oxide and oxygen in equal proportions.[9] The gas is self-administered by way of a mask and demand valve, provides moderately good analgesia, and has an excellent safety record. Entonox may be relatively contraindicated in patients with thoracic trauma (e.g., with pneumothorax) and those requiring an FiO_2 greater than 0.5. Unfortunately, Entonox is not yet commonly available in the United States and the ability to provide analgesia in the prehospital phase is limited. Alternatives include small doses of intravenous narcotic (e.g., morphine) titrated to effect, but concerns about the possibility of a head injury and the risk of respiratory depression restrict its widespread use. Ambulance personnel in the United Kingdom are trained in the prehospital use of intravenous nalbuphine, an agonist-antagonist opioid that provides excellent analgesia.

During interhospital or intrahospital transfers, some trauma patients, particularly those needing mechanical ventilatory support, require sedation. Patients who are paralyzed and heavily sedated are in effect receiving a general anesthetic during transport. This is commonly provided by continuous infusion of a benzodiazepine or narcotic or both, with or without a muscle relaxant. Propofol, an intravenous anesthetic agent, has recently become available in the United States and may prove to be an ideal drug for providing continuous sedation and anesthesia during transport of the trauma patient.

INTRAOPERATIVE CONCERNS

Monitoring

Reliable monitoring is a cornerstone of quality anesthetic care. Basic monitoring should begin in the admitting area (or more optimally in the field) and continue throughout intrahospital transport to and from the operating room and ultimately into the intensive care unit. Monitoring is used as a guide to physiologic homeostasis, response to therapy, and anesthetic depth. The extent and types of monitors used are dictated by the mechanisms and severity of injury as well as pre-existing medical conditions. Routine monitoring for any patient receiving a general anesthetic includes electrocardiography and recording of blood pressure, temperature, and breath sounds. Pulse oximetry and continuous end-tidal CO_2 monitoring have recently been added.

Various methods exist to monitor arterial blood pressure: Korotkoff sounds, automated oscillometric devices, and intra-arterial catheters. The presence of significant physiologic derangements in a trauma patient mandates invasive blood pressure monitoring, usually from the radial or femoral artery. In this way, accurate beat-to-beat assessment of blood pressure and the ability to sample arterial blood gases for respiratory, hematologic, and chemical analysis are made available.

Hypothermia is a significant problem in trauma patients, particularly in those who receive massive volume replacement without adequate prewarming. Side effects of severe hypothermia include inhibition of coagulation (particularly, platelet aggregation), dysrhythmias, and antagonism of nondepolarizing muscle relaxants.[63] Conversely, hyperthermia may indicate sepsis or, more rarely, a malignant hyperthermia crisis, because traumatic stress may be a triggering mechanism for malignant hyperthermia.[58] Core temperature is usually monitored via an esophageal probe, but rectal or nasopharyngeal probes also may be used. Esophageal probes have the advantage of providing a means of monitoring breath sounds.

Pulse oximetry is an invaluable monitor of cardiac and respiratory function. Arterial oxygen saturation (S_pO_2) reflects pulmonary gas exchange, whereas the waveform is a sensitive indicator of peripheral perfusion. However, due to the delay between alveolar hypoxia and desaturation of the peripheral blood, pulse oximetry should not be relied upon as an early warning device for hypoxemia (for example, after esophageal intubation).

Capnometry remains the most accurate means of detecting proper placement of the endotracheal tube.[15, 73] Because airway management in trauma patients is frequently difficult, the use of continuous end-tidal CO_2 monitoring is crucial. Such a device should be located in the admitting area of a trauma center.

A urinary catheter should be inserted, primarily to monitor urine output.[1] It is also a useful aid for the diagnosis of renal failure and transfusion reactions. In the absence of renal disease, urinary flow rate will reflect adequate volume replacement (assuming normal cardiac function).

A central venous pressure catheter will reflect right-sided cardiac pressures. In the absence of a disparity between the left and right sides of the heart, the central venous pressure catheter will also be a reasonably reliable indicator of left ventricular filling. However, in the presence of left ventricular dysfunction, a flow-directed pulmonary artery catheter is indicated to guide management intraoperatively and in the intensive care unit.[89]

Currently, neurologic monitoring under general anesthesia is still limited. When significant intracranial surgery is anticipated, continuous pressure monitoring via an indwelling device (e.g., intraventricular catheter, subdural bolt) is necessary.[38]

Intraoperative Fluid Management

Intraoperative fluid management is a continuation of the volume resuscitation begun in the field and admitting area. Essentially, volume, hemoglobin, and coagulation factors must be replaced. Rationally, a balanced approach can be undertaken. Crystalloid solutions (primarily balanced salt solutions) replenish extracellular fluids lost in association with hemorrhage. This extracellular fluid deficit results from third space losses and redistribution of fluids from extracellular spaces to intracellular spaces.[24] Such "third-spacing" is particularly associated with severe blunt trauma, in which microcellular damage is more extensive. Balanced salt solutions help restore the normal physiologic milieu by rapidly distributing across cell membranes.

Red blood cell transfusions, usually in the form of packed or resuspended cells, are used to replace preoperative and intraoperative losses. The primary goal of transfusion is provision of oxygen-carrying capacity to meet the oxygen requirements at the tissue level. Although a hemoglobin concentration of 10 g/dL has been touted as the "magic" level, recent changes in transfusion practices suggest that healthy patients may tolerate lower levels of hemoglobin if normovolemia is maintained.[99] This becomes an increasingly important consideration in view of present day concerns about life-threatening communicable diseases, such as AIDS and hepatitis. Conversely, adequate transfusion of blood in certain subpopulations of trauma patients (e.g., the elderly, patients with coronary artery disease, or those with sickle cell disease) must be performed judiciously.

In most trauma patients, coagulation defects usually have one of two causes: dilutional thrombocytopenia or Factor VIII deficiency.[29] Therefore, the indiscriminate use of fresh frozen plasma should be discouraged. Coagulation disorders should be diagnosed (with platelet counts, prothrombin time, partial thromboplastin time, and fibrinogen levels) and appropriate component therapy administered.

Anesthetic Plan

The choice of anesthetic technique depends on a multitude of factors, although in the seriously injured patient, the margin for error is smaller. Both regional and general anesthesia offer particular advantages and disadvantages.

In the appropriate patient, regional anesthesia permits the avoidance of intubation in a trauma patient who is at high-risk for aspiration, reduces the intraoperative stress response, provides excellent pain relief, and may be utilized in the postoperative period to facilitate rehabilitation. Several clinicians believe regional anesthesia is underutilized during the acute phase of injury.[19, 32] However, the sympathectomy caused by major conduction blocks may compromise the ability for cardiovascular compensation from blood loss. Therefore, regional blockade is probably best suited for isolated limb injuries and postoperative pain and rehabilitation. The value of regional anesthesia in trauma patients becomes most apparent in austere situations, such as refugee camps, battlefields, and mass casualty and disaster sites, where sophisticated equipment is in short supply and the shelf-life and limited volume of intravenous/volatile anesthetic agents preclude their extended use.[33]

The polytraumatized individual will most likely benefit from the cardiopulmonary control offered by general anesthesia.[95] Endotracheal intubation and mechanical ventilation provide airway protection, support breathing, and permit respiratory muscles to rest. Changes in intravascular volume from injury or surgical repair often occur in the traumatically injured patient; thus, general anesthesia facilitates rapid alterations in the depth of anesthesia to maintain optimal physiologic conditions.[94]

Hypnotic induction agents demonstrate enhanced potency in the presence of hypovolemia. This presumably results from concentration effects (in the hypovolemic intravascular space) and reduced clearance. Therefore, a reduction in dosage is indicated. Table 11 demonstrates useful regimens for induction of general anesthesia in a variety of clinical situations.

In the United States, sodium thiopental is the most important intravenous induction agent. In appropriate doses, its cardiodepressant effects are minimized.[37] It protects the brain by decreasing the cerebral metabolic rate for oxygen and cerebral blood flow, leading to an overall reduction in intracranial pressure.[38]

Other useful induction agents include ketamine, etomidate, and the benzodiazopines, particularly midazolam. Ketamine usually increases blood pressure and heart rate by releasing catecholamines.[107] However, it may produce hypotension in patients with exhausted sympathetic tone (e.g., if they are severely hypovolemic). Ketamine is contraindicated in patients with closed head injuries because of potentially dramatic increases in intracranial pressure.[38]

In hemodynamically stable patients, anesthesia is maintained with a potent inhalational agent administered in an oxygen or air/oxygen mixture in combination with an intravenous opiate.

Nitrous oxide has few specific indications in the intraoperative management of trauma patients, although it is very useful in the field (see earlier discussion of Entonox). It can accumulate in closed spaces, contribute to increased intracranial pressure, and cause myocardial depression.[38, 95]

Isoflurane appears to be the most useful inhalational agent. It is readily titratable, reduces intracranial pressure (in low concentrations), does not sensitize the myocardium to catecholamines, and shows no epileptiform activity on electroencephalography.

Muscle relaxation is maintained with a nondepolarizing muscle relaxant, usually vecuronium or pancuronium. Potent opiates, such as fentanyl and sufentanyl, help to reduce the concentration of inhaled anesthetic. They also provide profound analgesia and relative cardiovascular stability.

Severely injured patients are transported from the operating room to either the postanesthesia care unit or directly to the intensive care unit while still anesthetized. Mechanical ventilation should be continued until the patient is fully stable and has recovered from the central nervous system depressant effects of residual anesthetic agents. Postoperative problems can include the risk of aspiration on emergence, delayed emergence, emergence delirium, and the need to complete diagnostic evaluations. These are discussed elsewhere.[96]

CRITICAL CARE ISSUES

As stated in the introduction of this article, anesthetic care of the traumatized patient by the anesthesiologist continues into the intensive care unit. The third

Table 11. *Intravenous Anesthetic Drugs for General Anesthesia*

CONDITION*	HYPNOSIS	MUSCLE RELAXATION	ANALGESIA	AMNESIA
GCS-3, flaccid, unresponsive	None	None	None	None
Cardiac arrest	None	None	None	None
Shock, syst BP <80 mm Hg	None	Succinylcholine, 1.5 mg/kg or vecuronium, 0.28 mg/kg	Fentanyl, 0.5–1 μg/kg as needed or nalbuphine, 0.25–0.5 mg/kg	Scopolamine, 0.5 mg IV or midazolam, 1–2 mg if BP increases
Hypotension, syst BP 80–100 mm Hg	Thiopental, 0.3–1 mg/kg (titrate to effect) or midazolam, 0.1–0.3 mg/kg (titrate to effect) or ketamine, 1 mg/kg	Succinylcholine, 1.5 mg/kg or vecuronium, 0.28 mg/kg	Fentanyl, 1–2 μg/kg or nalbuphine 0.5–1.0 mg/kg	Midazolam, 1–2 mg if not used for hypnosis
Head injury, GCS 4–9 with hypertension	Thiopental, 3–5 mg/kg	Vecuronium, 0.28 mg/kg or succinylcholine, 1–5 mg/kg (if rapid postintubation motor examination needed)	Fentanyl, 1–2 μg/kg or sufentanyl, 0.1–0.2 g/kg	None
Combative, BP normal to elevated	Thiopental, 2–5 mg/kg (titrate to effect) or midazolam, 0.2–0.3 mg/kg (titrate to effect)	Vecuronium, 0.28 mg/kg or succinylcholine, 1.5 mg/kg	Fentanyl, 1–2 μg/kg or sufentanyl, 0.1–0.2 μg/kg or nalbuphine, 0.5–1.0 mg/kg (may require frequent redosing)	None Hypnotic drug will usually suffice

From Stene JK: Anesthesia for Trauma. *In* Miller RD (ed): Anesthesia, ed 3. New York, Churchill Livingstone, 1991; with permission.
*GCS = Glasgow Coma Scale score; syst BP = systolic blood pressure.

peak in trauma-related mortality (see Fig. 2) involves those patients who survive initial resuscitation and operative intervention. The major cause of morbidity in the Intensive Care Unit is sepsis with resultant adult respiratory distress syndrome (ARDS) and multiple organ failure. However, a subtle phenomenon must be appreciated. As noted earlier, because of the improved prehospital care of trauma patients, greater numbers of severely injured patients are presenting to trauma centers with increased morbidity. Because of improved preoperative and intraoperative care, more trauma patients are surviving the perianesthetic period and populating critical care areas. Yet, hidden within the third (late) peak of trauma deaths is a group of patients whose care during the initial Golden Hour and early anesthetic phase is good, but not good enough. Metaphorically "breathing a sigh of relief" when the patient's systolic blood pressure reaches 90 mm Hg is not sufficient. Early aggressive invasive monitoring, traditionally used to guide focused therapy toward more meaningful parameters, such as tissue oxygen delivery and consumption, with the goal of quickly bringing them within appropriate ranges, must now become the standard of care. In this way, the third peak of deaths can be reduced.

As critical care management continues to improve, the TA/CCS must be prepared for the large number of intensive care unit patients who will return to the operating room for repeat procedures. Anesthesia for patients with ARDS and multiple organ failure needs to be delivered through a ventilator capable of generating high minute volumes in the presence of high airway resistance and poor lung compliance. Because most standard anesthesia machines are incapable of such performance, an intensive-care-unit–type ventilator (e.g., Siemens 900C) is necessary. If only a traditional critical care ventilator is available, the TA/CCS may choose to alter the anesthetic plan, for example, decide to provide total intravenous anesthesia.

Adult Respiratory Distress Syndrome

Severe ARDS is characterized by diffuse bilateral infiltrates on radiography of the chest, hypoxemia, hypercarbia, and poor pulmonary parenchymal compliance.[6] The use of pulmonary artery catheters has demonstrated elevated pulmonary artery pressures without evidence of left ventricular dysfunction.[92] Coagulation abnormalities consistent with disseminated intravascular coagulopathy also may be present. The etiology of ARDS is extensive and encompasses sepsis, aspiration, pulmonary contusion, massive transfusion, and fat emboli, all of which are related to distinct sequelae of injury and its management. The diagnosis of ARDS is often delayed until significant hypoxemia and pulmonary infiltrates mandate mechanical ventilation. The degree of hypoxemia appears to correlate well with mortality.[92] Those patients responsive to mechanical ventilation and positive end-expiratory pressure appear to have a greater chance of survival.[61]

Damage to the pulmonary vasculature, the primary site of injury, results in a capillary leak syndrome. There is no clear explanation for the development of vascular damage. Oxygen-free radicals released from neutrophils that infiltrate into the interstitial space or that adhere to pulmonary endothelium may have a significant role.[82]

Because sepsis is a primary cause of ARDS, management efforts should be concentrated on the identification and treatment of infection. Supportive care remains the mainstay of the management in ARDS patients. Extracorporeal membrane oxygenation and CO_2 removal may avoid oxygen toxicity and barotrauma while giving the lungs time to heal.

Sepsis and Multiple System Organ Failure

Recent advances in critical care have improved the treatment outcome for patients with single organ failure. As the level of care continues to improve and patients survive the initial insult and early postoperative complications, various combinations of multiple organ failure are becoming more common. The mortality from multiple organ failure ranges from 30 to 95%, depending on the systems involved.[40]

Among other aspects, the immune system of the trauma patient is altered. Almost all elements, including cellular immunity, lymphocyte numbers, neutrophil chemotaxis, and reticuloendothelial cell function, are diminished.[74] The trauma patient is at high risk for sepsis, and as the hospital stay lengthens, the risk of nosocomial infection from monitoring and life-support systems increases.

At the MIEMSS Shock Treatment Center, during a 7-year period, 1407 of 10,308 patients (14%) sustained 2310 infectious complications.[100] The vast majority of infections were from gram-negative bacilli (67%); gram-positive bacteria accounted for 44% of infections, and anaerobes and yeast, 9% and 1.5%, respectively. Mortality from pneumonia and intra-abdominal infections was greatest.

That same study revealed an 11% incidence of phlebitis and a 3% incidence of arterial-line infection. Most catheter-related infections result from the patient's resident flora, usually, *Staphylococcus* species. Therefore, the TA/CCS must emphasize the importance of aseptic technique during all line placements.

The pathophysiology and therapeutic management of sepsis and multiple organ failure are beyond the scope of this article but have been reviewed extensively.[25, 38, 39, 64, 75]

Infection leading to ARDS and multiple organ failure, with their high rates of morbidity and mortality, requires careful yet aggressive management of the critically ill polytraumatized individual. Undoubtedly, a greater understanding of the physiologic alterations secondary to traumatic insult is needed to improve survival and quality of life.

THE FUTURE OF TRAUMA ANESTHESIA

Based on at least two of the authors' experiences (KJA, CMG) at several prominent United States' trauma centers, the lack of involvement of anesthesiologists early in the trauma patients care has resulted in a multitude of problems. For example, after the admission of a patient sustaining major trauma, an anesthesiologist is not often called to the emergency department until airway and resuscitation management has been attempted by emergency medicine physicians who find the circumstances beyond their capabilities. Thus, the anesthesiologist inherits a complex situation that has been created iatrogenically and is compounded because airway management equipment and drugs are not reliably present in the emergency room.

In even worse scenarios, the anesthesiologists on call may receive a phone call placed by a clerk informing them that a seriously injured patient is en route to the operating room via the elevators. Typically, no information regarding cardiovascular or respiratory status or any of the management that has been undertaken will be available. The patient arrives several minutes later without an airway or adequate intravenous access. The operation begins while these deficiencies are frantically addressed by an entire team of anesthesiologists.

Such scenarios occur all too frequently as a result of outdated communication systems and the fact that anesthesiologists, to a large extent, are still not considered part of the formal trauma team in the United States and, thus, are not routinely informed when trauma patients enter the emergency medical services pipeline. Steps to correct such deficiencies might include better communication between the anesthesiology departments and emergency departments of various trauma centers, as well as opening lines of communication between anesthesiologists and the field providers of emergency medical care at a municipal administrative level. In some centers, such steps are already being taken.

In 1988 the International Trauma Anesthesia and Critical Care Society (ITACCS) was incorporated as a professional society to further the development of anesthesiologists as traumatologists, to be a forum for anesthesiologists to share ideas and techniques for managing trauma patients, to address issues that relate to subspecialists who dedicate a significant portion of their professional effort to the anesthesia and critical care of trauma patients, and to provide an educational framework to train the TA/CCS.[45] Increased involvement of anesthesiologists in trauma care and in ITACCS will lead to the development of protocols for trauma anesthesia and other improvements in trauma management.[97]

As of May 1991, ITACCS has produced four successful symposia as part of the Annual Trauma Anesthesia and Critical Care Symposium Series. A summit symposium, also sponsored by ITACCS, in conjunction with the 10th World Congress of Anesthesiologists and other academic and professional organizations is scheduled to take place in June 1992 at the Hague, Holland. ITACCS is also developing a dedicated training program—the International Trauma Anesthesia and Critical Care Fellowship—to be conducted at various trauma centers around the world. ITACCS has, together with certain members of the Anesthesiology Department of the University of Maryland, formed a working group known as LOTAS (Level One Trauma Anesthesia Simulation). The goal of LOTAS is to use task analyses, decision trees, and video analyses of actual management of trauma patients to produce a realistic computer simulator for use in teaching trauma anesthesia and resuscitation. Simulation permits intellectual, psychomotor, and decision-making skills for management of traumatized patients to be learned without risk to patient safety and will complement any clinical training the junior anesthetist receives.

As part of this project, an international survey of trauma anesthesia has been circulated to trauma anesthesiologists around the world. The purpose of this survey is to identify the varying roles of trauma anesthesiologists and to use the information to establish a data base for the LOTAS project.

Adequate research in trauma anesthesia has thus far been deficient; another function of ITACCS is to reverse this trend.

SUMMARY

The specialty of trauma anesthesia and critical care redeveloped in response to the need for quality care of the injured. Trauma currently ranks fifth in overall mortality in the United States. Its impact upon society is even more dramatic in terms of the years of potential life lost and total financial losses. Regionalization of trauma care and the development of sophisticated trauma centers have positively impacted on mortality. As a result, late trauma deaths from sepsis and multi-organ failure are gaining more attention. The TA/CCS has emerged as an individual dedicated to the continuity of care necessary for the optimal management of trauma patients. Initial evaluation, resuscitation, and intraoperative care represent only a portion of the TA/CCS role. Critical care transport and intensive care management are extensions of the prehospital and perioperative phase of care. The future of trauma anesthesia and critical care is promising and challenging. Under the auspices of ITACCS, critical care of the trauma patient will continue to improve.

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Ethics in the Intensive Care Unit

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Ethics is defined as "the discipline dealing with what is good and bad and with moral duty and obligation."[30] Patients present daily with illnesses that require the health care professional to consider ethical questions as well as diagnostic and therapeutic ones. Often these ethical concerns are asked and answered on an intuitive level only. Health care workers (especially physicians and nurses) in the intensive care units are facing increasingly complex medicolegal concerns and questions, such as the rationing of health care, withdrawing or withholding of care, and disagreements between the patient and patient's family and the physician, making it important that they reflect on the ethical aspects of their decisions, which require a critical instead of simply an intuitive approach to ethical problems.

PRINCIPLES RELATING TO MEDICAL ETHICS

Autonomy, beneficence, nonmaleficence, and justice are four of the basic principles within medical ethics. Autonomy, or patient self-determination, has become more important in recent years. Individuals are generally more aware of medical issues than they were in the past, and, thus, patients are more willing and, indeed, anxious to take part in health care decisions.

This change is illustrated by the recent reactions of medical professionals to the Jehovah's Witness decision not to receive blood or blood products because of religious beliefs. Health care workers respect this decision, even though it limits their therapeutic options, because of the patient's circumscribed right to determine his or her fate. The concepts of informed consent and refusal require that the health care professional acknowledge this point. A legal parallel for this principle is Supreme Court Justice Benjamin Cardozo's statement in 1914 that "Every human being of adult years and of sound mind has a right to determine what shall be done with his body."[32]

On the other hand, beneficence and nonmaleficence direct health care workers,

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respectively, to help their patients and to do no harm. These principles form the basis of trust in the physician-patient relationship.

The concept of justice directs health care workers to provide medical care to all who are in need in an equitable manner. Any rationing of health care must be impartial and consider the ramifications to persons of different socioeconomic and age groups.

NEED FOR ETHICAL THINKING

Within the framework of the doctor-patient relationship, situations are bound to arise that result in conflicts between the just mentioned principles. An example previously alluded to is the Jehovah's Witness. Frequently, situations arise in which in the physician's best judgment, it is necessary to transfuse blood due to a life-threatening state. Jehovah's Witnesses believe that "life" or the "life force" is present in blood and that they risk losing "external life" and being shunned by God if they receive banked blood.[3, 21, 22] Thus, although the principle that respects the patient's autonomy requires that the physician forego transfusion and perhaps as a consequence allow the patient to die, respecting the patient's decision puts the physician in conflict with both the principles of beneficence and nonmaleficence. Similar conflicts occur within the realm of critical care medicine. Physicians frequently do not have any formal training in ethical reasoning to help resolve these conflicts; merely attempting to enforce one or another of these principles or to utilize intuitive analyses often leads to inadequate or controversial solutions to an ethical dilemma. Understanding moral reasoning may help the physician in these difficult situations.

MORAL THEORY

Facts Versus Values

Given correctly gathered empirical data, a statement of fact is either true or false. This is not so in regard to values or evaluative principles. Values promote that which is good and discourage that which is bad, but they are neither true nor false.

Although it should seem quite simple to distinguish a fact from a value, in many situations the two may be confused. In the case of the Jehovah's Witness who hemorrhages to a hematocrit of 4%, which is incompatible with life, it is a fact that the Jehovah's Witness has a low hematocrit. The patient's need for enhanced oxygen-carrying capacity to sustain life is also a fact. It is a fact to the physician that the patient needs a red blood cell transfusion to sustain life and further, that the correct response to a hematocrit of 4% is to transfuse blood. However, some of these facts also presuppose a value judgment that the physician makes because he or she values life above all else. The Jehovah's Witness, although agreeing that the hematocrit is 4% and that death will occur if oxygen-carrying capacity is not enhanced, would still refuse a transfusion regardless of the hematocrit or the probability of dying. The suggestion to Jehovah's Witnesses that a transfusion of blood is needed to preserve life involves a violation of principles concerning their temporal life, which they consider to be a transitory preparative stage for an everlasting life. If the Jehovah's Witness were to accept a transfusion, it would be a violation of a religious rule for which he or she would lose the chance of everlasting spiritual life.[23]

The ability to distinguish between disputes about facts and those about values is important to the doctor-patient relationship and may significantly impact on patient well-being. Of course, some patients may hold certain beliefs due to incorrect information. When educated about their disease and treatment, this latter group of patients may agree to follow the physician's recommendations. This change does not come about because of a change in the patient's morals but because of medical education. It is the health care worker's responsibility to determine whether lack of education about a disease or a different set of values is the cause of patient noncompliance. It is not acceptable, however, to simply dismiss the patient's values or preferences because they differ from the physician's.

Consequential Versus Nonconsequential Ethical Theories

Two commonly used ethical theories in Western culture are utilitarianism and the idea of rights. Recently, some moral philosophers have worked to unify these two.[18] Classical utilitarianism is often associated with David Hume, Jeremy Bentham, and John Stuart Mill, all of whom wrote in the late eighteenth and early nineteenth centuries. The idea of human rights originated in social contract theories of the seventeenth and eighteenth centuries.

Utilitarianism is a moral theory which holds that "there is one and only one basic principle in ethics, the principle of utility, which asserts that we ought always to produce the greatest possible balance of value over disvalue."[4] The utilitarian thus looks at the consequences of an action and determines the overall good—the value—that it brings to the persons involved. The goodness of a principle or action is thus related to the positive net effect it has on the greatest number of concerned persons.

The notion of rights, which is also called a deontologic ethic because it emphasizes the principle of duty over utility, is a nonconsequential approach to ethics. The notion of rights in ethics stresses that certain actions are wrong even if the consequences are beneficial. Thus, a theory of rights would stress justice over utility or assert limits on actions no matter how attractive, desirable, or beneficial.

The difference between these two theories can be shown through the example of euthanasia, if it is considered from the perspective of the physician. When applied to the physician's situation, the utilitarian approach does not begin with the principle that killing is wrong, but only with the simple principle of utility plus the empirical knowledge that has been gained about various situations. Normally, killing is wrong because it clearly harms individuals. However, when confronted with a patient who has a widely metastatic neoplasm causing terrible and untreatable pain and who has requested that his or her life be ended quickly, the utilitarian would hold that euthanasia would serve that patient's interests and thus be justified. In this situation, the greater utility for any other patient in a similar situation would be in allowing the patient a quick, painless death. An ethical theorist who stressed rights and obligations, however, would hold that the act of a physician killing a patient is wrong no matter what the results and no matter what the patient requests. The purpose of insisting that a right or principle is at stake is to establish a constraint on decision making. The argument is that without such a definite restriction on euthanasia, physicians will find themselves on a "slippery slope" leading to a willingness to kill patients for convenience or prejudice. However, in this case the argument from principle was specified from the physician's perspective. It is possible for a theory of rights to defend a patient's suicide on the basis of some unqualified right to one's own existence and body. Thus, the bare statement of these two theories of ethics does not obviate further reflection on moral reasoning.

Critical Versus Intuitive Thinking

In critical reflection, an individual takes the time and has the freedom to analyze moral assumptions. Furthermore, the thinker can speculate about moral decisions and experiment with moral reasoning. Health care workers are often called upon to act in situations in which there are conflicts of values. By using critical moral thinking, they can better prepare moral intuitions for times of crisis.[18]

Drawing further on the euthanasia example, what should the physician do about this patient assuming that the patient-physician relationship is a strong one? If this is not the case or if the patient and physician do not know one another, the options are severely limited. Should the physician assist in the demise of the patient? The principle of respecting the patient's autonomy and always stressing beneficence would argue that the answer is yes. If the patient-physician relationship is strong, the physician, patient, and patient's family members will have discussed at some point during the patient's illness the options for dying. Some individuals want to watch every sunrise they are able to no matter what pain is involved. Others want to pass out of this world as soon as possible. Thus, if euthanasia were at all justifiable, it would have to be responsive wholly to the patient's preferences.

What should be done when the patient requests help with his or her death but the physician feels morally compromised in providing this? If the case is unfolding in the emergency room, the only option for the health care team is to make every attempt to save life and limb. On the other hand, if over a period of time the patient makes his or her fundamental preference known to the physician, if that preference is to opt for an assisted death, and if the physician would be compromised in doing so, the physician ought to withdraw and leave the patient in the care of a designated colleague. In a nonemergency situation, if the patient cannot expect that his or her fundamental moral preference will be carried out, the physician must take a strong paternalist position, namely, allow health care workers to substitute their values for the patient's. This position is, as we have argued elsewhere,[23] unacceptable from a practical and a moral standpoint and would lead to the destruction of the bond of trust that links practitioner and patient.

Physicians have the duty to argue with and confront their patients on these issues. The attempt to dissuade another person from a choice is yet another aspect of the use of critical as opposed to intuitive thinking. The assertion that all fundamental moral preferences should be treated as equal is itself an ethical principle; but these preferences can and perhaps should be criticized. Indeed, one way to challenge a patient's intuitive moral preference is to begin by assuming the equality of all preferences and then to analyze the justification for the patient's choice. One need not agree with the patient's specific moral preferences to acknowledge them. However, when a patient's basic moral choices are questioned, argument should not lead to coercion.

Rationing Health Care

Health care spending in the United States is said to be increasingly burdensome to the economy. In 1987, 11.4% of the gross national product or $511 billion was spent on health care,[15] almost three times the proportion of the gross national product spent in 1950.[24] Of these moneys, 15% was used for intensive care services.[6] Several factors have been associated with the rise in health care expenditures: technologic imperatives, inefficiency of supportive services, and an aging population.[2] The cost spiral may be unsustainable. Multiple cost containment measures have been attempted and are currently in place, although their effectiveness is controversial. One solution to the cost spiral that has been advocated is some form of rationing.[2] The United States has experienced rationing by lack of access. There are currently 30 to 37 million people in the United States who have no access to health care.[31] Most of these individuals are working minimum wage jobs, do not qualify for Medicare or Medicaid, do not have private insurance, and, therefore, cannot afford medical care. There are strong moral objections to a method that rations purely on the basis of socioeconomic status and disregards equity.

Aaron and Schwartz[1] define another type of rationing, a system in which "not all care expected to be beneficial is provided to all patients." The National Health Service of England is often cited as an example of this type of rationing. Because of inadequate levels of funding, British physicians are placed in a position in which they decide who is to receive a specific treatment that exists in limited supply.[2] These physicians perform the difficult and ethically complex function of "gatekeeping."

The physician as gatekeeper is a recently described concept.[32] We believe that it most probably is not an appropriate role for physicians. When a physician undertakes the care of a patient, the doctor-patient relationship requires that the physician do everything in his or her patient's best interest without regard to cost.[17] This principle of advocacy is an understood, if often unstated, part of the relationship. If patients thought that the decisions their doctors made were colored by economic considerations, the trust in the doctor-patient relationship would be undermined. This principle does not mean that the physician must do absolutely everything possible for the patient, only that he or she strive to provide the ill individual with all of the services that are in the patient's best interest. To maintain the integrity of the physician-patient relationship, the gatekeepers, if they must exist and if they are physicians, should only be those individuals who do not function as direct patient caregivers.

With a relatively fixed number of intensive care unit (ICU) beds currently available, health care workers in this area must decide who will and who will not be admitted.[36, 41] There are several ways to make such decisions. Medical facts decide many of the conflicts, but the scientific data are often inadequate, and, thus, ethical decisions must frequently be made. Because intensive care consumes a significant portion of the health care budget, more efficient ways to utilize ICU resources are continuously sought. Keeping the terminally ill out of the ICU or arguing that individuals with selected diseases or above a certain age should not be admitted to the ICU are only some of the ways that "efficiency" is sought. The issue of age and health resource limitations has been argued by many prominent medical ethicists. They suggest that if each person has a limited amount of health care assets at his or her disposal, the individual would be wise to direct the use of those assets over the earlier years of his or her life to receive the most benefit. On the other hand, Levinsky[25] argues that care should be allocated according to expected benefit to the patient regardless of age. He uses the example of a productive 85-year-old artist with pneumococcal pneumonia and no other life-threatening disease. By what convoluted logic would it be right to deny the artist ICU care because he is 85 years old when there is a good chance of recovery to a productive life? Indeed, leaving aside the cultural bias against old persons, we find data indicating that age, in and of itself, is not a predictor of poor outcome. Chalfin and Carlon,[10] for example, found that older critically ill cancer patients in the ICU had a lower mortality rate than that of the younger patients. These authors reviewed the records of all cancer patients admitted to the ICU over a year. The patients younger than 65 years had a higher proportion of systemic malignancies, whereas those 65 years and older had primarily solid tumors. The length of stay was the same for the two groups, but the average severity of illness was less for the 65-and-older group and, as mentioned previously, the mortality was lower. Thus, age by itself is not an adequate parameter for exclusion from ICU care. In selected instances, age may be one of several factors considered when admission to the ICU is contemplated, but it should never be the only criterion. Furthermore, the principles of patient autonomy and the physician's duty of beneficience, no less than justice, must have major roles in any contemplated rationing plan.

Acquired immunodeficiency syndrome (AIDS) has spurred several controversies with respect to critical care. The economic impact of AIDS on the individual involved and on the country's economy are considerable. With the first 10,000 cases alone occurring in the United States, a median postdiagnosis survival of 392 days was noted. Caring for these individuals consumed over $6.3 billion.[17] After diagnosis, these patients spent a mean of 168 days in the hospital at a cost per patient of $140,000 or approximately $800 per day. The lost income per patient was $490,000. Review of more recent data shows that the average cost per patient has decreased to approximately $80,000, primarily because of an increase in outpatient treatment.[8] AIDS has been, and still is, considered an ultimately fatal disease. However, therapeutic progress has prolonged the time between infection with the human immunodeficiency virus (HIV) and the first opportunistic infection. Pneumonia caused by the protozoan *Pneumocystis carinii* is one of the most common infectious complications of AIDS. The mortality rate of patients with *Pneumocystis carinii* pneumonia and respiratory failure necessitating endotracheal intubation and mechanical ventilation has been as high as 85%. More recently with aggressive treatment, mortality rates in the hospital and not just in the ICU have declined in some situations to 60%.[13] Furthermore, postdischarge follow-up suggests a 1-year survival rate of 75% (CM Franklin, personal communication).

When the rationing of ICU care is considered, some may argue that patients with AIDS should either not be admitted at all or that some stage of the illness should be specified after which admission should be denied. This system might be defended on the grounds that the patient's state is ultimately terminal in as much as there is little hope of meaningful survival even if he or she is treated aggressively in the ICU. One frequently hears, although rarely sees in print,[33] the notion that because some persons with AIDS live an unconventional lifestyle, their disease is self-inflicted, and, thus, the patients have no "claim" on ICU resources.

None of these arguments withstands ethical evaluation. Although there are persons with AIDS who prefer not to have aggressive ICU care at their stage of the disease, this decision must be made with and not for the patient. A large percentage of patients have considered the pros and cons of ICU care and desire it.[35] With the recent improvement in the survival of patients with the most severe form of *Pneumocystis carinii*, it cannot be argued that the situation is completely hopeless. The principle of beneficence would indicate that these patients deserve at least the option of ICU care. The argument that the disease is self-inflicted cannot be used unless all persons with self-inflicted diseases are also denied ICU care. If as a society we opt to limit care to smokers with lung cancer or to alcohol abusers with cirrhosis and massive gastrointestinal tract bleeding, we might consider limiting care to individuals with AIDS. Of course, the "self-inflicted" argument is a *non sequitur* when AIDS is considered globally. What treatment should be given to patients with AIDS due to blood transfusions or cryoprecipitate use?

Withdrawing or Withholding Therapy and Living Wills

Terminal care decisions in the ICU are commonly made and are often wrought with ethical and legal implications. The ethical principles discussed previously may help physicians, patients, and their families to arrive at appropriate care decisions. In this section, we discuss the ethical ramifications of withholding or terminating life support.

Considering the type of patient being seen is the first step in solving the dilemma. Veatch[38] described four classifications of patients involved in terminal care decisions. The first group encompasses patients who are competent. Courts have consistently permitted these patients to decide their own course. One example is the Jehovah's Witness who refuses lifesaving blood transfusions. These patients are exercising their right of autonomy. The physician has a moral obligation to educate these patients about the consequences of their decision but cannot force them to accept a treatment they do not want. The patient may ethically refuse treatment, in the case of the Jehovah's Witness, because of religious beliefs that make the treatment overly burdensome. Patients may also refuse on the grounds that the treatment is useless.

The second group of patients includes those who are incompetent but who hold and have expressed when they were competent preferences concerning life and its termination. This group may contain individuals in a persistent vegetative state who have previously expressed their wishes not to have life supported artificially should they ever reach such a state. The ethical principle affecting decisions for these patients is also autonomy.

The Massachusetts Supreme Judicial Court ruled in 1986 that the feeding tube could be removed in the case of Mr. Brophy, a 49-year-old man who after unsuccessful surgery for a ruptured basilar artery aneurysm was in a persistent vegetative state, because he had indicated while he was competent that he wished never to be kept alive by artificial means. The court ruled on three concepts.[34] The first of these was that Mr. Brophy had a right to refuse artificial feeding because he would have refused such life-sustaining treatment had he been able to express himself. The second was that by upholding the patient's right to refuse treatment, the court would not be allowing suicide but, rather, would be letting the underlying disease take its natural course. The third was that the physicians involved would not be forced to stop the artificial feeding if they felt morally compromised in doing so, but they would be obliged to facilitate transfer to another institution or to another physician's care where the patient's preference could be honored. The court stated that withholding and withdrawing artificial life support should be considered the same. This understanding has been echoed by medical ethicists.[39] The line of reaasoning involves the fact that the reasons for withdrawing treatment are often the same as those for withholding it and, therefore, should not be treated as morally different. A potential problem with giving more consideration to withdrawing treatment is that some health care professionals may hesitate to start it knowing they may have to face the decision to later withdraw it. However, in our experience, this concern has not been an issue.

Another group of patients includes those who have never been competent and have no one to speak for them because of lack of interested family members. In this situation, the course of action must follow the principle of beneficence. Usually, a court-appointed guardian must be designated to make decisions in the best interest of the patient. The *Saikewicz* case, discussed later, is an example of this situation.

Patients in the fourth group are incompetent but have an interested and loving family. This group includes those patients who had never expressed any wishes pertaining to therapy while they were competent. Veatch[39] argues that in this situation the family need not necessarily do what is most objectively in the patient's best interest but may choose what they believe is in the patient's best interest. If the family is believed to be going far beyond what is reasonable, a surrogate may be appointed. What becomes abundantly clear with this classification is that the physician is never the person making the final decision. The patient or his or her surrogate are the true sources of authority for decision making. The physician acts as an educator for the decision-making individual, presenting the options for and against treatment and facilitating the decision.

Directives for initiating or withdrawing treatment may be provided in a living will. As of 1986, 35 states had passed legislation recognizing living wills and natural death directives as legal documents.[16] Honoring the living will is an extension of the principle of respecting patient autonomy. The document speaks for the patient when the latter is unable to express his or her wishes, which can occur after the onset of dementia, a debilitating stroke, an accident resulting in a persistent vegetative state and other situations. Living wills help in many instances, but they can also become problematic by using terms such as "extraordinary," "heroic," or "imminent" that are difficult to define precisely. What is considered extraordinary? What is heroic? How imminent does death have to be to be "imminent?"

Eisendrath and Jonsen[11] presented a case in which a very active elderly woman completed a living will indicating that if she should be left without reasonable expectation of recovery from a grave physical or mental disability, no artificial means or extraordinary measures should be used to keep her alive. The woman underwent a carotid endarterectomy and, although initially doing well, later suffered a massive stroke that left her paraplegic and aphasic. Aspiration pneumonia then developed that ultimately required nonemergent tracheostomy for continued care. Knowing the content of her living will and considering the extent of her debilitation, the patient's brother questioned this care. He persisted in his questioning, and the case was taken to the hospital's ethics committee. They recommended that treatment be continued because they were unsure exactly what the patient wanted. Because of the ambiguity, they believed they should err on the side of treatment. Over the next several months, the patient recovered a significant portion of her previous health and expressed her satisfaction with the ethics committee's decision.

Despite some confusion as to the patient's moral preference, the committee opted to invoke the principle of beneficence in choosing life-sustaining treatment. This should, of course, be done whenever doubt exists as to exactly what the patient desires. Exceptions to choosing treatment arise when the burden of treatment outweighs the benefits or when there is no hope of recovery. The latter is the basis for the court ruling in the *Saikewicz* case.

Mr. Saikewicz was a 67-year-old, severely mentally retarded man who had lived in a state institution most of his life. Although physically strong, he had no communication skills except for gestures and physical contact. Mr. Saikewicz became ill with an acute leukemia. His guardians at the state institution debated whether to allow him to be treated with a chemotherapeutic regimen that might prolong his life for as much as a year. After discussions with the patient's physicians, they believed that the course of chemotherapy would cause Mr. Saikewicz considerable suffering and that he would probably require multiple transfusions, none of which he would understand. They were concerned that he might need to be restrained or sedated to complete the chemotherapy. Although the patient had two sisters, they declined to become involved. The institution then sought a court-appointed guardian to make decisions regarding this case because they were unsure as to the correct course of action. The court-appointed guardian reviewed the case and decided against treatment. The court agreed, basing its decision on the ethical principle that extraordinary measures should not be used when, after careful medical scrutiny, death is determined to be the only expected outcome.

When Patients and Physicians Disagree

Another problem that occasionally arises within the critical care setting is a disagreement between patient and physician with respect to treatment. Patients may refuse life-sustaining treatment or they or their families may request withdrawal of treatment. Less frequently, patients or their families may request therapy that is potentially inappropriate. Health care workers involved with the patient, physicians as well as nurses, may disagree with the patient's decision based on moral grounds. Hospital policy may not allow withdrawal of certain forms of life-sustaining treatment. The ethical principles involved in all of these cases are patient autonomy, beneficence, and justice. On what moral grounds can patients refuse life-sustaining treatment? When do the state's rights take precedent over an individual's rights? When does the principle of beneficence attain greater importance than the patient's right to autonomy?

Veatch[39] argues that in the case of the competent patient, there are several morally defensible positions for refusal of therapy by the physician. If the treatment has no benefit, it is useless and may be refused. This principle also applies to the situation in which a patient or a patient's family requests a useless therapy. The other ground for refusal is if the treatment presents a great and overwhelming burden for the patient. The same treatment can be a grave burden for one patient but not for another, depending on that person's frame of reference. These positions also may be extended to the group of always incompetent patients who have caring and loving families and to the group of incompetent patients who have previously made known that they do not want artificial life support. When health care workers or institutions disagree with the patient's request or refusal, the courts often become involved. The courts have considered the individual's right to autonomy but have also described at least four reasons for the state to enforce treatment. These are as follows: (1) it would be upholding the standards and values of the medical profession to do so, (2) it is preserving life, (3) it is preventing suicide, and (4) it is protecting dependents.[7] The first three have frequently not been considered compelling reasons.

In several cases, the courts have found that the patient's wish should be honored over the objections of the physician and the institution. The physician and institution were required to continue care of these patients even though they requested to have the patients transferred to the care of others not ethically opposed to the patient's preference.[29] In the case of Mr. Brophy, discussed previously, the physicians were directed to facilitate transfer so that they would not have to carry out orders conflicting with their morals. In all of these cases, the courts determined that the principle of patient autonomy outweighed the principle of beneficence. Although the preservation of life is believed to be crucial, in many cases the courts have cited the criterion of uselessness of further treatment and grave burden to the patient to allow withdrawal of life support. In the *Conroy* case[20] the New Jersey Supreme Court rejected the argument that terminating life support was tantamount to suicide by differentiating between self-destruction and self-determination. The court stated that individuals have the right to terminate life support and thereby allow the underlying disease to take its natural course. They recognized that termination of life support fulfilled the patient's preference to live free from medical support and pain.

One situation in which the courts have ruled that the patient must undergo treatment is in cases in which there are dependents who may upon the death of the patient become wards of the state. Such situations may arise when a Jehovah's Witness who is a single parent of minor children refuses livesaving blood transfusions.

Not all instances of disagreement go to the courts, nor should they. Although there are many disagreements in medicine, in ideal circumstances, these should rarely occur because of the trust within the patient-physician relationship. When disagreements arise, careful consideration needs to be given to the possible causes of the dispute, such as whether it stems from a lack of patient education or a misunderstanding concerning what is in the patient's best interest. These questions need to be addressed in all patient-physician interactions.

When Health Care Workers are Afraid

Numerous historical examples can be cited in which health care workers have placed their own health at risk in caring for patients.[27, 37] These examples include the great plagues in the fourteenth through seventeenth centuries in Italy, the epidemics of yellow fever in the eighteenth and nineteenth centuries in the United States, the treatment of pneumococcal pneumonia before the discovery and distribution of antibiotics, the treatment of patients with tuberculosis, and, presently, the treatment of patients with AIDS. Is there a moral obligation for physicians to treat patients who have potentially or definitely lethal diseases for which there is no known cure? What are health care workers' obligations when the etiology or mode of transmission or both of a potentially lethal disease is unknown? Are they obliged to put their own lives at risk?

In past epidemics there have been a variety of responses by health care workers. Some workers fled the plagued cities, some either refused to treat critically ill patients or charged much higher fees to treat them, and still others put their lives at grave risk by caring for the infirm.[12] Fox[12] notes that some physicians who chose to treat patients may have done so not out of ethical, religious, or personal virtue, but because of the financial opportunities available to them if they complied. Some physicians were offered contracts to work in plague hospitals and, if they survived, were given excellent positions afterward. Some were forbidden to leave their cities; others fled with those to whom they usually provided health care. Similar situations occurred in the United States during outbreaks of yellow fever and cholera. Once antibiotics were available and the modes of transmission for the diseases were determined, the question of whether there was an obligation to treat patients no longer had to be addressed, at least until more recently with the onset of AIDS.

In the United States, physicians are free to choose their patients. Once they have established a physician-patient relationship, the physician continues to care for that patient unless the former does not have the expertise for a specific problem or identifies another physician whom the patient is willing to see. A physician is not required to take care of a patient with whom a relationship has not been established. Thus, by choosing their patients carefully, physicians can avoid those with illnesses they do not wish to treat.

Even if physicians are legally free to chose their patients, are they also ethically free to refuse patients? What is a physician's ethical responsibility to the public? What if a patient under a physician's care acquires AIDS and the physician is afraid to continue treatment for fear of being afflicted? For a period of time after the initial cases of AIDS were described, the mode of transmission of this disease was not known. Health care workers recognized AIDS as an almost uniformly lethal syndrome and were afraid to treat these patients. Is fear adequate moral grounds to refuse to treat patients with AIDS?

In their chapter on beneficence, Beauchamp and Childress[4] discuss the concept of obligatory beneficence. They state that "The positive benefit that physicians and other health-care professionals are obligated to seek is the promotion of health, as defined in part by the patient's own values." To benefit others is a laudable moral goal. Taken to the extreme, it can cause severe destitution of the persons giving of themselves, their money, and their life. Although this action would be morally praiseworthy, most would argue that there is a limit to obligatory beneficence. Beauchamp and Childress[4] write

> We would argue that apart from special moral relationships such as contracts, X has a determinate obligation of beneficence toward Y if and only if each of the following conditions is satisfied and X is aware of the relevant facts: (1) Y is at risk of significant loss or damage; (2) X's action is needed (singly or in concert with others) to prevent this loss; (3) X's action (singly or in concert with others) has a high probability of preventing it; (4) X's action would not present significant risks, costs, or burdens to X; and (5) the benefit that Y can be expected to gain outweighs any harms, costs, or burdens that X is likely to incur.

If a patient is under a physician's care and AIDS develops, there is a contractual agreement that the doctor will continue to care for that patient unless it can be shown that it is not within his or her expertise to do so. In that case, the physician should "act in concert with others" to benefit the patient.

With the restrictions outlined above, within the principle of obligatory beneficence the only morally defensible reason to withdraw from the patient's care is if the health care worker can show that caring for the patient would present significant risk, cost, or burden to the health care worker. However, in our opinion, even in the initial period after the AIDS virus was first recognized, this risk was not significant. During this time, there was great uncertainty about how AIDS was spread and concern about a possible epidemic. With the additional information obtained on patterns of transmission, we now know that the overall risk of contracting HIV from occupational exposure is low, especially if the precautionary guidelines outlined by the Centers for Disease Control are followed. The risk of acquiring AIDS from a patient is, in fact, lower than the risk of acquiring hepatitis B.[9, 14, 40] In their prospective study of health care workers with occupational exposure to HIV, Henderson et al[19] found that of 2712 cutaneous exposures to infected patients' blood, only one person became infected after a parenteral exposure, and no infections were reported to have occurred after cutaneous or mucous membrane exposure. When this group of investigators combined data from all studies, the risk of transmission from a percutaneous exposure was 0.3% per exposure. Others also have found that the risk of infection is low, especially with strict adherence to universal precautions.[5, 26, 28] The group at highest risk are nurses rather than physicians.

When the very low risk to health care workers is considered, AIDS is somewhat dissimilar to the epidemics of the past. Physicians during the great plagues might have had a sound moral argument against treating patients by citing the stipulations of the theory of obligatory beneficence outlined previously. The same argument is less applicable in regard to AIDS because the risk of infection is so low even when universal precautions are not used. With this information in mind, we do not believe a moral argument can be made for allowing physicians to refuse to treat patients with AIDS who are in need of medical care.

SUMMARY

Health care workers in the ICU frequently confront ethical dilemmas. We recommend that they use moral reasoning rather than intuitive analyses to resolve these dilemmas. Specific recommendations are

1. If a patient expresses a wish based on religious or moral values that is contrary to the proposed course of treatment and if the patient makes that wish known while competent, his or her wish should, in nearly all cases, be respected.
2. If the administration of a hospital wishes to institute a rationing policy to conserve ICU resources, that policy should not withhold care on the basis of socioeconomic status, age, or presumptions about patients with a particular disease.
3. If health care workers are fearful of providing care to patients with a contagious and fatal disease such as AIDS, they should recognize that their risk of infection is quite low and that, more importantly, they have an ethical obligation to treat the patient in their care.

Although we believe that moral reasoning can be helpful in deciding these complex issues, the importance of a strong physician-patient relationship cannot be overstated. Only communication between doctor and patient can reveal the exact nature of disputes about treatment and provide the basis for the most appropriate resolution of ethical dilemmas.

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The Intelligent Anesthesiologist's Guide to the Language and Logic of Allocation

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Once upon a time, in the not so distant past, clinical allocation was relatively easy—medical resources were matched to meet patient's medical needs, and outside of some inevitable red tape, physicians could safely delegate to others the task of financing the resources they consumed. As we approach the twenty-first century, this blithe unconcern with resources seems increasingly to be associated with a semi-mythical past. Today, hospitals are operating in the red, Intensive Care Units are constantly full, elective surgery is always at risk for cancellation or rescheduling or both, and the ambulance can be turned away from the emergency room door. Suddenly, a set of concerns that at one point seemed out of place in the acute care hospital have become part of the physician's working life. With these concerns comes the need to master a new language, one more at home in the halls of academe than in the corridors of the clinic—the language and logic of allocation, the language of bioethicists, economists, philosophers, and policy analysts.

In this article, a philosopher-physician-policy analyst team attempts to make the current language of allocation accessible to physicians and to introduce them to some ideas and arguments in academic and policy analysis circles. For the sake of convenience, we have chosen the glossary format as our vehicle for covering the subject from "A" to "Z" or rather, from "Admission/Discharge Criteria" to "Von Stetina." The list we compile is supplemented by an extensive bibliography representing the literature we have found useful in our research on allocation and rationing. Whenever possible, we have attempted to refer to literature that should be accessible to the physician.

To the best of our knowledge, this is the first attempt to prepare even an abbreviated glossary of allocation terminology for physicians. Undoubtedly, there is room for improvement. Our hope and intent is that anyone with suggestions as to how to improve on our effort will communicate them to us directly so that we may refine this glossary in the future.

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A GLOSSARY OF IDEAS AND TERMS RELEVANT TO ALLOCATION

Admission/Discharge Criteria for the Intensive Care Unit. As the population ages inexorably, the increasing demand for access to expensive high-technology medical care directly conflicts with the decline in available resources. In many situations, when there have been no formal guidelines, this has resulted in admissions to already filled hospital emergency departments and critical care units (see Von Stetina entry) and less than optimal care. This can and has impacted adversely on patient care, outcomes, and the moral of hospital staff, both nurses and physicians. All too often, the responsibility of whether to admit patients has been defaulted to nursing staff[32] as the available on-site decision-makers. Physicians acting as both the critical care unit directors responsible for triage and as patient caregivers are caught in a position of conflicting interest. On one hand, they are responsible for the level of care being provided to the current residents of the Intensive Care Unit. Alternatively, they also may be responsible for maintaining a given level of accessibility to the unit for both elective and emergency care. Satisfying the responsibility to individual patients may and often does conflict directly with meeting communal/societal responsibilities.

To bring a sense of order to what may be a difficult and ethically confusing decision-making process, demand has arisen for the formalization of admission and discharge criteria used by decision-makers to establish a sense of logic and uniformity to the process. The first problem in doing so has been setting the degree of specificity of the admission and discharge criteria. Administrators, regulators, and legislators have a deep-seated affinity for highly specific and detailed rules and criteria. Unfortunately, clinicians and patients exist in a gray world of uncertainties and random events in which excessively specific guidelines may prove more problematic than useful. Guidelines that are too general, however, may prove to be of little value. The Society of Critical Care Medicine has produced a set of general guidelines that may be used as a starting point for institutions when developing their own criteria.[31]

The other equally significant problem has been developing a clear and consistent protocol that defines the identity, responsibility, and authority of the decision-makers. The decision-makers must be politically independent, knowledgeable about triage, staffing, and patient case load in the critical care units, and have a working relationship of companion units, such as the emergency department, postanesthesia care unit, step-down units, and other special care areas. Admission and discharge criteria are of little value unless the lines of authority and responsibility are clearly drawn, and willing and capable individuals are identified to carry them out.

Advanced Directive. An advanced directive is a legal instrument, such as a "do not resuscitate" order or a living will, which directs caregivers to initiate or to discontinue anticipated medical interventions. As Baker[4] and other commentators have observed, in the absence of advance directives, intervention is the default option in hospitals in the United States. The impact of advanced directives, therefore, is to limit resource utilization to those patients who actually desire the intervention—in effect, the least onerous form of rationing.

Ageism, Ageist. Ageism is morally unjustifiable discrimination on the basis of age. The rhetorical pattern is similar to that of racism or racist, and sexism or sexist.

Age Rationing. Age rationing is any allocation of scarce resources in which chronological age, per se, is considered relevant. The classic example is the British National Health Service policy of refusing to provide organ transplants and kidney dialysis for patients older than 60 years, even when patients have a high probability of benefiting from the intervention. In this policy, age is a criterion for allocation but not a prognostic indicator; allocation schemes that consider age as a prognostic indicator are not regarded as forms of age rationing.

The fundamental moral question raised by age rationing is whether the scheme is ageist, i.e., whether it constitutes an unjust or immoral form of discrimination. Although the received opinion has been that age rationing is necessarily ageist, in recent years a number of eminent commentators have challenged the conventional wisdom. Among the most notable challengers are Daniel Callahan, Director of the Hasting Center for Bioethics,[5-7] Norman Daniels,[9] and Robert Veatch, Director of the Kennedy Institute of Ethics.[35, 36] Daniels has developed a *Rawlsean* analysis of age rationing in which it is argued that were each of us placed behind a "veil of ignorance" and asked to choose a pattern of rationing medical care that distributed limited medical resources throughout our lives, we would allocate the bulk of the resources toward the younger portions of our lives. Age rationing is thus a form of rationing that we would opt for ourselves (were we to choose from a position of reflective equilibrium), and, hence, Daniels argues that age rationing cannot be unjust.

Allocation, Aliquot (de facto, explicit, implicit). An allocation is a pattern in which resources are distributed; an aliquot is a unit of the resource being distributed. Allocations may be part of an explicit rationing scheme, or the rationing may (de facto) be implicit but unstated in the scheme. Among the various forms of allocation in common use are market allocation (i.e., allocation by price), merit allocation (e.g., the priority given to service-connected disabilities in Veterans Administration hospitals), and queue allocation (first-come, first-served).

APACHE, MPM, TISS, etc. In an attempt to understand the heterogeneous populations cared for in critical care units, a veritable "alphabet soup" of scoring systems has been developed over the past two decades. With the advent of prospective payment systems (diagnostic related groups) and the increased competition for declining resources and funding, appropriate categorization of patients, identification of case-mix ratios, and resource utilization management have become paramount. For the most part, generalized case-mix classification systems, although acceptable for most medical and surgical patients, prove to be inadequate for critical care unit populations. Consequently, several distinctly different tools have been developed to assess critically ill patients. The most prominent of the tools are as follows:

—APACHE: Acute Physiology And Chronic Health Evaluation. This originated as a severity-of-illness scoring system and now revised as APACHE III, also functions as a survival probability score. This score depends on data collected within the first 24 hours following admission to the Intensive Care Unit.[18, 19] The APACHE prediction of survival has been validated at the 85 to 88% reliability level. A multicenter trial is underway to improve and validate the reliability of APACHE III.

—MPM: The Mortality Prediction Model (MPM) is a statistical model that utilizes 11 objective variables at the time of admission to the Intensive Care Unit. This model has been validated in the literature, and its reliability in terms of predicting survival is comparable to that of APACHE.[22, 33] A multicenter study is underway to improve the reliability of the MPM by tracking a small number of variables over time. Twenty-four and forty-eight hour models are being validated while a seventy-two-hour model is under development.[23]

—TISS: The Therapeutic Intervention Scoring System (TISS) is a weighted tool that assigns 1 to 4 points to each of 76 possible medical and nursing interventions. This score is designed to be collected every 24 hours and is a measure of resource utilization. Consequently, TISS relates to costs and should, but does not necessarily, relate to the severity of illness. This tool was originally designed in the early 1970s and has been periodically revalidated.[8] It has been used to establish nurse-patient staffing ratios and the costs of care.

Other more specialized systems have been developed, such as the Injury Severity Score for trauma patients, the Glasgow Coma Score for head injured patients, and pediatric scoring systems, to name a few. How these tools will be utilized is the subject of growing controversy, as is the issue of their reliability and generalizability. These tools can probably be used effectively to establish case-mix ratios, cost-effectiveness, and eventually to measure quality of care and performance in the Intensive Care Unit. The unanswered questions, however, are whether these tools can or should be used in the management of the individual patient as well as in the assessment of aggregate populations, can or should these tools be used to make triage or admission decisions, and can or should these tools be used to terminate the care of already hospitalized patients. Although it is generally agreed that at present, these devices might well be used by physicians in their discussions with the families of patients, most recognize the potential for abuse. The need for objective assistance in the decision-making process of triage and termination of life support is one that is constant and most likely to grow in the presence of an environment that is increasingly litigious, regulated, and whose resources are declining.

Cost-Containment. Cost-containment encompasses literally any effort to constrain the growth of costs, including efforts to eliminate unnecessary care or care without benefit. More controversially, cost-containment may involve a judgment that "the benefit of additional care to an individual may not be worth the added resource costs in terms of what those resources could do if used in some other way."[3] Daniels[10] argues that it is easier for providers to contain costs by rationing beneficial services in the United Kingdom than in the United States because the fixed medical budget in the former guarantees that resources denied one patient will be reallocated to another patient who might derive more benefit. In contrast, in the United States, resources saved from limiting the provisions of marginally beneficial care may not be applied to the care of other patients.

Cost-Effectiveness and Cost-Benefit Analysis. Cost-effectiveness and cost-benefit analysis includes formal analytical techniques for comparing the negative and positive consequences of alternative procedures or interventions. Although both cost-effectiveness and cost-benefit analyses measure the costs of the intervention, only cost-benefit analysis measures the positive consequences in terms of dollars, for example, by placing a monetary value on the worth of a life saved or on days of disability averted. In contrast, cost-effectiveness analysis measures benefits in terms of the number of disability days averted, years of life saved, or years of quality-adjusted life-years added. The term *cost-effectiveness* is sometimes used broadly to include both cost-effectiveness and cost-benefit. Both types of analysis can be used to set priorities among competing claims to a fixed budget. By rank-ordering the incremental cost-effectiveness ratios of various medical procedures, decision-makers can give priority to procedures that maximize net health benefit for a given budget. One example of such a plan is the Medicaid initiative proposed by the state of Oregon (see Oregon Health Care Rationing Initiative entry). Detsky and Naglie[11] have published a guide explaining cost-effectiveness analysis and how it can be used to rank-order medical procedures.

Equity, Equality. Equity or equality means allocating a resource equally in the sense that every individual gets the same care relative to some measure (e.g., medical need, dollar amount, and so forth).

Intensive Care Unit Entitlement Index. Englehardt and Rie[13] have proposed an index that ranks entitlement to Intensive Care Unit admission, discharge, and discontinuation of treatment as a method of developing explicit resource allocation policies. Entitlement is a function of the following equation:

$$\text{ICU Entitlement} = \frac{\mathrm{PQL}}{\mathrm{C}},$$

where P indicates the probability of the successful outcome; Q, the quality of success; L, the length-of-life remaining; and C, the costs required to achieve therapeutic success.

This proposal is controversial. Commentators question (1) the appeal to costs; (2) the ability to measure the quality of life; (3) the age-rationing implicit in the length-of-life remaining measure; and (4) the use of the entitlement index to disentitle patients to care (especially to life-sustaining interventions) without the consent of the patient or the family.

Intensive Care Unit Medical Director as Gatekeeper. Both the Joint Commission on the Accreditation of Healthcare Organizations[16] and the Society of Critical Care Medicine[31] require that a medical director or designee prioritize admissions and discharges to an Intensive Care Unit when beds are fully occupied. This gatekeeper role conflicts with the more traditional medical role of the physician as an individual patient advocate. In the United States, ethical and legal constraints make the dilemma implicit in these role conflicts especially acute. One solution to the dilemma is to divorce the gatekeeper role completely from the patient care role. Mulley[26] and Zawacki[42] have suggested the election of an Intensive Care Unit physician triage officer to act as a societal resource allocator, leaving other physicians free to advocate for their patients.

Market Allocation. Market allocation advocates that care is given to each individual according to his or her ability to pay (or to have a third-party payer) from caregivers according to their desire and ability to sell their services for pay.

Marxian Allocation. Marxian allocation advocates that care is given, "From each according to his ability, to each according to his need." A bit of reflection should reveal this as the standard system of allocation for patients admitted into an acute care setting; health care personnel allocate as much resources as they can to meet the patient's medical needs. Rationing consists of any constraint on this "ideal" arrangement.

Maximin Allocation. Maximin allocation is a term commonly used in Rawlsean analysis in which resources are allocated to minimize the worst outcomes. This is a common insurance practice (insuring against worst outcomes) and contrasts radically with utilitarian, cost-benefit, risk-benefit, and cost-effectiveness approaches.

Medical Futility. Medical futility is the characterization of a particular medical intervention as incapable of producing any measurable medical benefit, e.g., being hopeless, impossible, improbable, terminal, or useless. There is no standard usage in the medical literature. Schneiderman et al[30] refer to Greek mythology and the daughters of Danaus, condemned in Hades to drawing water in leaky sieves. An example of a statutory definition of medical futility is the New York State Law controlling the writing of do-not-resuscitate orders. Medically futile is defined to mean that cardiopulmonary resuscitation will be unsuccessful in restoring cardiac and respiratory function or that the patient will experience repeated arrest in a short period before death occurs.[2] Determinations of medical futility are often cast as probabilities. Schneiderman et al[30] propose

> that when physicians conclude (either through personal experience, experience shared with colleagues, or consideration of published empiric data) that in the last 100 cases a medical treatment has been useless, they should regard the treatment as futile. If a treatment merely preserves permanent unconsciousness or cannot end dependence on intensive care medicine, the treatment should be considered futile.

Some critics argue that only the patient can judge whether the probability of successful resuscitation and the resulting quality and length of life is so low that treatment should be foregone.[41] Others argue that physicians, in exercising a value judgment, should unilaterally decide to withhold interventions such as cardiopulmonary resuscitation.[34, 27]

Oregon Health Care Rationing Initiative (Oregon Basic Health Services Act). In 1989 the Oregon legislature enacted a policy expanding Medicaid coverage to all uninsured persons with incomes below the federal poverty level ($10,560 for a family of three in 1990). Budget constraints usually limit Oregon's Medicaid coverage to those persons living at 60% of the federal poverty level or lower. The Oregon Health Services Commission, an independent body, is ranking medical treatments and diagnostic tests from the most beneficial to the least beneficial using a comparative analysis of the costs, benefits, and clinical effectiveness to determine which services would be provided at the 100% level. Measures of benefit include the values of health outcomes discussed in the Quality-of-Life Measures entry. In the context of a fixed budget, the basic minimum Medicaid benefit package would be constructed from the procedures at the top of the list. Thus, prenatal care might be included, whereas liver transplants would be excluded (depending on the amount of funds allocated in the annual budget). The proposal contains a "liability shield" protecting providers for not providing excluded services. Critics of the Oregon proposal claim that poor women and children are singled out as the only groups to suffer from rationing (including the denial of procedures that could make the difference between life and death).[14] Proponents claim that many residents of Oregon (those between the 60th and 100th percentiles of the federal poverty level) are already being denied basic health care. At the time of this publication, the federal government has not yet given its approval to the Oregon initiative. Before the anticipated national debate can take place, Oregon must first complete the priority listing and submit it to the Health Care Financing Administration of the United States Department of Health and Human Services.

Painful Prescription. In a book entitled *The Painful Prescription* examining the health care systems of the United States and the United Kingdom, Aaron and Schwartz[1] note the painful choice facing the United States:

> The United States can suffer a continual increase in medical expenditures and in expenditures yielding benefits worth less than costs. Or it can impose effective limits. If it follows the second course, it will have to confront a long list of hard decisions on which discussion has not yet begun. Rationing will inevitably be a painful prescription.

Practice Guidelines. Practice guidelines are "official statements or policies of major organizations and agencies on the proper indications for performing a procedure or treatment or the proper management for specific clinical problems."[40] Practice guidelines are also known as practice policies, practice parameters, and practice standards. The impetus for practice guidelines is partially cost-containment and partially quality assessment. (We now realize from studies of geographic variation in the rates of procedure use that many "standard" interventions appear to be ineffective or inappropriate.) Methods for creating practice guidelines are described in an on-going column by David Eddy appearing in the *Journal of the American Medical Association* in volumes 263 and 264.

Ideally, practice guidelines should contain a quantitative estimate of the health and economic outcomes of the intervention in terms of its benefits, harms, and cost (see Cost-Effectiveness and Cost-Benefit Analysis entry). Wennberg[38] suggests that when patients are informed of the benefits, harms, and cost of various treatment options, they might attach a lower value to the outcomes of certain relatively standard invasive, high-technology interventions, i.e., that physicians are overutilizing these types of interventions. Eagle et al[12] have reported an example of the development and use of practice guidelines in the Intensive Care Unit.

Several agencies and organizations are involved in the development of practice guidelines, including the Agency for Health Care Policy and Research (United States Department of Health and Human Resources), American Medical Association, various specialty societies, Blue Cross and Blue Shield Association of America, Health Insurance Association of America, and RAND Corporation.

Quality-of-Life Measures. Quality-of-life measures ascribe numerical values to health outcomes, for example, to individual lives and expected future lives. A common measurement is the quality-adjusted life-year, which is a summary statistic that incorporates the mortality and morbidity effects of a particular medical intervention. If, for example, an additional year of healthy life is valued at 1 year, an additional year of less-than-healthy life would be valued at less than 1 year (depending on the extent of morbidity, disability, and discomfort). As a measure of effectiveness, the quality-adjusted life-year can be incorporated into cost-effectiveness analysis to help establish priorities for funding.

La Puma and Lawlor[20] question the use of quality-of-life measures as guidelines for resource allocation and raise the following questions:

—Can quality-of-life be measured accurately and used?
—Is utilitarianism an acceptable moral philosophy?
—Are equity and efficiency compatible?
—Can projections of community preferences substitute for individual preferences?
—Because the elderly have less capacity to benefit than the young, is this ageism?
—Will physicians use quality-adjusted life-years as clinical maxims?

Currently, the Quality-of-Well-Being scale,[17] which is similar to the concept of quality-adjusted life-years, is being proposed as the basis for rationing health care services in Oregon. Mulley[25] has published a general critique of the methods used in measuring and aggregating the preferences and utilities of individual patients.

Rationing. In any context of scarcity, i.e., in which resources are insufficient to meet desires or needs, rationing is any scheme or mechanism designed to restrict resources to match a limited but prioritized set of desires or needs. The paradigm case is a quota system that limits entitlements to food (rations). Medical care is considered to be rationed in any context in which patients or those with medical needs do not receive all the care that could possibly benefit them. Although Reagan[29] prefers to reserve the term to describe "the administrative distribution of goods, outside the market, that have suddenly become physically scarce," rationing criteria have traditionally included both price (market) and nonprice mechanisms, e.g., queueing or first-come, first-served, the ability to benefit medically, and social worth.[3]

Rawls, Rawlsean. Rawls or Rawlsean philosophy is a theory of justice developed by the Harvard philosopher John Rawls that is based on the premise that social policies and institutions should be assessed in terms of whether they could be subscribed to as part of a social contract to which everyone could agree, were it contracted from behind a "veil of ignorance."[28] The veil blinds each contractor to his or her actual position in society, as well as to facts such as their race, creed, religion, age, physical health, and talents, thus, guaranteeing the neutrality of fairness of the social arrangements or principles accepted in the contract. Rawls argues that contractors will distinguish between primary goods, or rights, which will be allocated on the basis of strict equality, and secondary goods, which could be allocated unequally, provided that the inequalities benefit everyone and attach to positions open to all. Rawls himself never applies his analysis to issues of health care, however, a number of other analysts, most notably Norman Daniels[9] and Robert Veatch,[35, 36] have applied his theories to the medical context.

Standards of Care. In common law, liability is determined by three factors: duty, dereliction, and direct causation. Malpractice exists if it can be demonstrated that a health care provider was derelict in a duty, and that this dereliction directly caused harm to a patient. The standard of care is used to determine whether a health care provider had a duty to provide a certain level or type of care. In medical malpractice litigation, the jury determines the standard of care that should govern physician conduct. Determination is based on testimony as to what a competent physician would do under comparable circumstances to the defendant physician.

The standard of care is traditionally seen as an incentive to the physician to maintain a minimum level of quality and not to withhold necessary care. The definition of the standard is usually independent of concerns about cost-containment and societal efficiency. As cost-containment pressures and resource scarcity increases, however, many individuals question whether standards can continue to ignore economics. Morreim[24] argues that courts and physicians, in their role as patient advocates, will most likely not depart from patient-centered standards. Therefore, legislation will be required to move toward any standard that might deprive individual patients of beneficial services, however small, based on resource considerations. Hirshfeld[15] has published an overall discussion of the topic.

Triage. Although "triage" is often used to characterize any form of clinical rationing, in the technical sense, the term is properly applied only to those forms of rationing scarce medical resources that prioritize resources according to differential medical impact. The term triage derives from the French term for "sorting" and was invented by Baron Dominique Larrey (1766–1842), Napoleon's surgeon general, as a scientific improvement on the prevailing system of queue allocation (first found or brought to the surgeon, first treated) because it radically decreased the casualties suffered by the French army.[21] Triage allocation schemes are most commonly employed in emergency, disaster, and military medicine; these schemes allocate resources to those casualties who, if left untreated, are likely to die or to suffer extensive morbidity but who are likely to live (without extensive morbidity) if treated. Lower priority is given to casualties who are likely to die despite treatment and to casualties who are likely to survive regardless of treatment.

There are two theoretical models of triage. First, it is possible to regard it as a maximin system of allocation designed to prevent worst outcomes or second, as a utilitarian scheme designed to maximize benefits.[39]

Utilitarianism (utilitarian, utility). Utilitarianism is a philosophical approach to ethics developed by Jeremy Benthan (1748–1831) and John Stuart Mill (1806–1873) that analyzes the morality of actions or moral principles in terms of outcomes (or utiles). In early formulations, these outcomes were often conceptualized in terms of pleasure or pain or happiness. Contemporary utilitarians prefer to use narrowly focused utility measures, such as quality-adjusted life-years or quality-of-well-being. Critics of utilitarianism question its adequacy as a moral theory on the grounds that it leaves out such important dimensions of morality as conscience, character, and duty, sacrificing all considerations about "means" for "ends" or outcomes. John Rawls and his followers argue that utilitarianism is an inadequate social theory because it makes no provision for human or civil rights and generates no defensible theory of justice.

Veil of Ignorance. See entry at Rawls.

Von Stetina V. Florida Medical Center. Susan Von Stetina, a young accident victim recovering from a successful operation, was admitted to an overcrowded Intensive Care Unit. She suffered brain damage when she was accidentally disconnected from a ventilator. It was brought out in court that Intensive Care Unit staff could have been made more staff available for care if two newly arrived patients had been transferred to another facility and a near-brain-dead patient had been discharged to the regular floor.[37] The case, decided in favor of Von Stetina, has been used frequently to support the argument that hospitals should perform triage based on the probability to benefit from intensive care (see report by Englehardt and Rie[13]).

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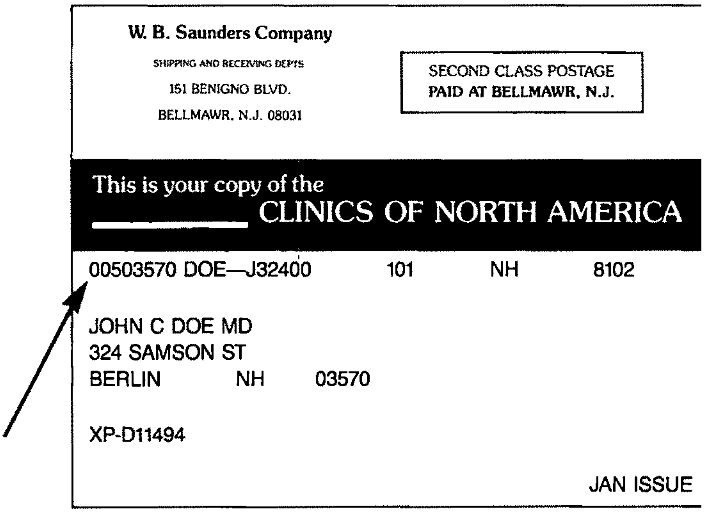

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